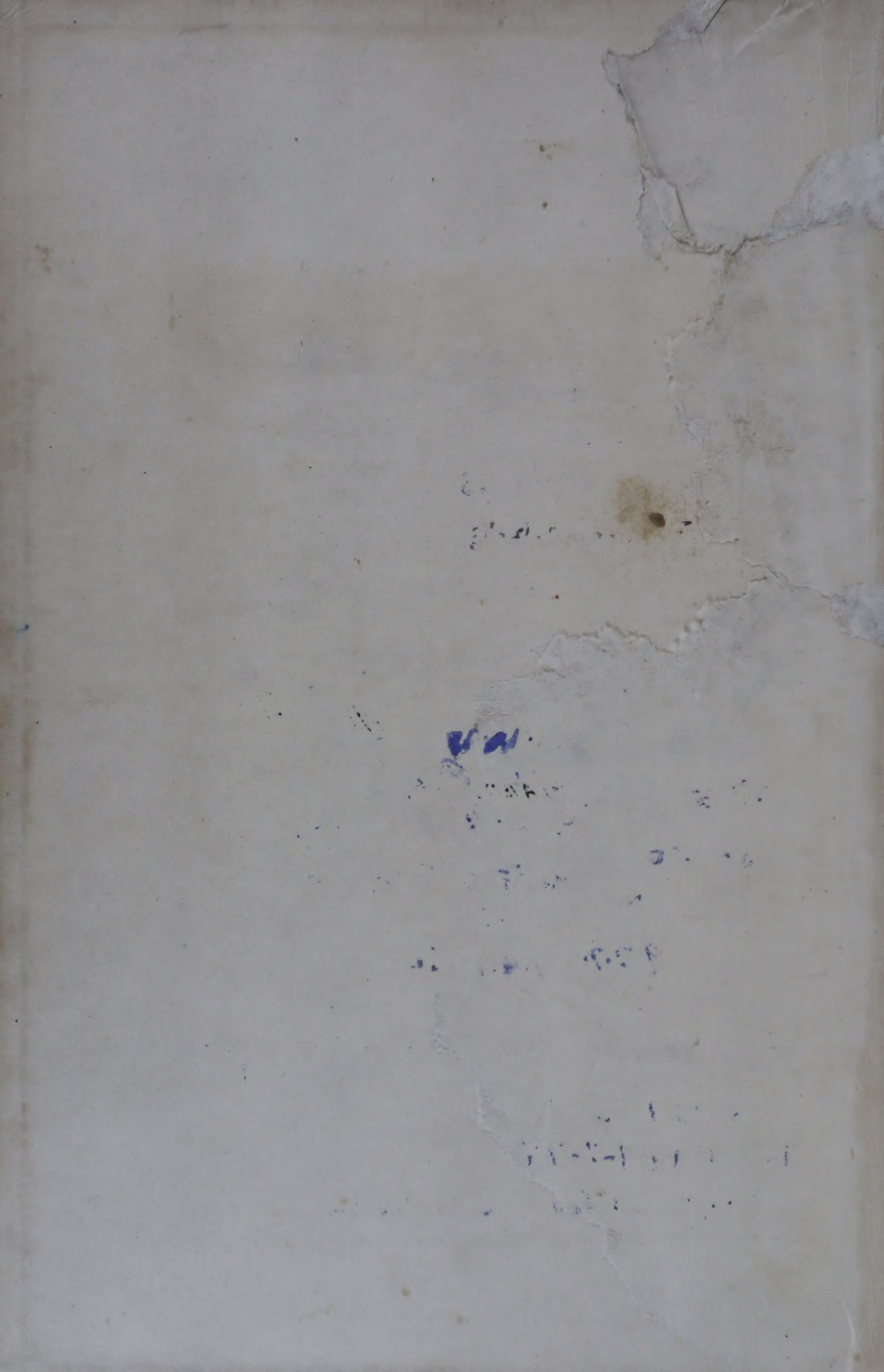


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1. alimentary tract diseases
2. cardiac diseases
3. blood forming tissues
4. endocrine glands
5. reproductive organs
6. nervous system
7. musculoskeletal system

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1. nutrients
2. macromolecules
3. inflammation
4. tumors
5. wounds
6. living agents
7. diseases
8. infectious diseases
9. bacteria
10. physical agents
11. chemical
12. deficiencies
13. pregnancy
14. obstruction

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A TEXTBOOK OF PATHOLOGY

SECOND EDITION

*Pathologic Anatomy in Relation to
the Causes, Pathogenesis, and
Clinical Manifestations of Disease*

BY ROBERT ALLAN MOORE

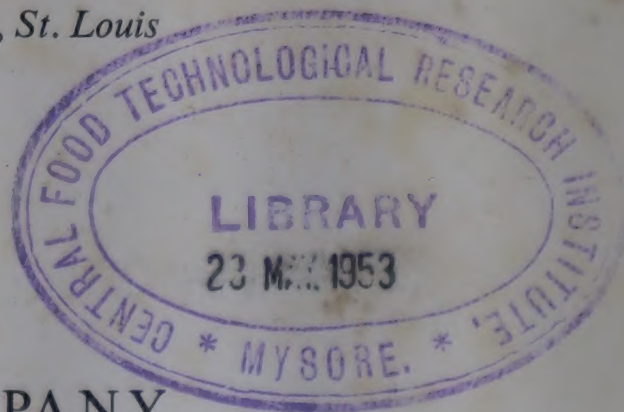
Edward Mallinckrodt Professor of Pathology

Washington University School of Medicine, St. Louis

Illustrated

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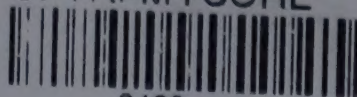
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CFTRI-MYSORE



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Textbook of pat.

TO
MY WIFE
AND
THE WIVES OF MEDICAL STUDENTS

*without whose faith there would
be fewer physicians in America*

Preface to the Second Edition

The cordial reception given to the first edition of this textbook by both pathologists and clinicians, the helpful comments of many colleagues, and the decision of the publisher to reset the type, have combined to make possible an extensive and thorough revision.

The additions, deletions, substitutions, and changes may be reviewed in eight categories.

1. The addition of new chapters in order to round out the subject matter. There are new chapters on such subjects as "Disturbances in the Metabolism of Enzymes," "General Considerations of the Infectious Diseases," and "Diseases Peculiar to the Aged."

2. Subdivision of some longer chapters. The chapter on diseases caused by viruses has been divided into three chapters: dermatropic, viscerotropic, and neurotropic. The chapter on the alimentary tract has also been divided into three chapters: oral cavity and esophagus, stomach and duodenum, and intestine. The neoplastic and non-neoplastic diseases of the skin have been placed in separate chapters.

3. Rearrangement of chapters to improve correlation. In the first edition diseases of the kidney were discussed in three different chapters. These have now been brought together.

4. Rearrangement of chapters to take into account changing concepts. The previously scattered diseases which apparently are closely related because of primary effect on mesenchyme—the collagen diseases—are now collected into one chapter. Similarly the newer concept of the demyelinating encephalitides has led to arrangement in a single chapter.

5. Relocation of certain sections because of new information. The clear demonstration of a virus in epidemic hepatitis, in pretibial fever, and in Colorado tick fever, for example, has resulted in transfer of the discussion to the chapters on viral disease.

6. Addition of sections on topics or diseases inadvertently omitted in the first edition. Examples in this category include rubella, thalassemia, synovioma, and fibrous dysplasia of bone.

7. Addition of sections on topics or diseases which were unknown or did not appear to deserve attention at the time of the earlier edition. Many changes and additions have been made on this basis, for example, Cox-sackie virus, rickettsialpox, viral diarrhea, effect of neutrons, effect of an atomic explosion, folic acid and vitamin B₁₂, retrolental fibroplasia, relation of rubella to congenital anomalies, and infectious lymphocytosis.

8. Revision of subject matter because of new or changing information. There are few sections which have escaped some change on the basis of this principle. A few examples are: hypoxic nephrosis (lower nephron disease), forward and backward failure of the heart, the unity of the malignant lymphoblastomas, adrenal insufficiency in the newborn, cystic and proliferative lesions of the breast (chronic cystic mastitis), granular cell neurofibroma (myoblastoma), and chronic (idiopathic) hypochromic anemia.

No attempt has been made to substitute systematically new references for old references unless information or ideas have changed or a new article in a widely distributed journal contains an up-to-date review. Most of the new references are to articles published since 1944.

Many friends and associates have assisted in the revision. I wish to thank particularly

Dr. Zola Cooper
Dr. Edward B. Smith

for their help on the chapters on diseases of the skin and on diseases of the blood forming tissues respectively. My other associates in the department of pathology at Washington University have made many useful suggestions

Dr. Margaret G. Smith
Dr. Lauren Ackerman
Dr. Gustave J. Dammin
Dr. Frank J. Dixon, Jr.
Dr. David E. Smith

As with the first edition, a search of the literature would not have been possible without the assistance of the staff of the library of the school under the supervision of

Miss Marion Murphy

Although no one person has served as an editorial alter ego, the secretaries in the dean's office and in the department of pathology have been most helpful.

Louise Jacoby
Dorothy Rinderer
Elizabeth Streeter
Helen Hendrix
Marjorie Lawson

A number of the younger members of the staff of the Department of Pathology assisted in the preparation of the index:

Dr. Fred T. Caldwell, Jr.
Dr. Margaret A. Carter
Dr. Menard C. Ihnen
Dr. Ruy Perez-Tamayo
Dr. James C. Roberts
Dr. Dale M. Schulz
Dr. J. D. Wheeler

The staff of the W. B. Saunders Company have been most considerate and cooperative despite delays occasioned by the press of my duties in other activities.

Once again my family have been tolerant and understanding of the many evenings, week-ends, and holidays spent away from home.

ROBERT A. MOORE

Saint Louis
June, 1951

Preface to the First Edition

Pathology occupies a pivotal position in the medical curriculum. Anatomy, biochemistry, physiology, and bacteriology are prerequisites. Clinical medicine and surgery follow it. In pathology the student must learn to apply the facts and theories of anatomy, biochemistry, physiology, and bacteriology to an elucidation of the causes, processes, and effects of disease. He must learn to reach ahead into the clinical branches of medicine and correlate the anatomic and physiologic changes with the signs and symptoms in the patient. He must learn to study the causes of disease with a view to prevention and control. Finally he must gain a clear understanding of the alterations in form and disturbances of function that take place in disease, so as to be ready for the next step in his medical education—the so-called “clinical years.”

Medical education is at the graduate level of university teaching. The students have completed two to four years of college. In this textbook I have attempted to present the subject in a manner consonant with the objectives of higher education. I have tried to avoid being dogmatic, and yet present to the reader clear concepts. The presentation of controversial material is intended to stimulate rather than to confuse, and by including it I have hoped to cultivate in the mind of the student a speculative and reasoning approach to the subject. The answers to the questions “Why?” and “How?” are as important as the answer to the question “What?” Specifically applied to pathology “Why?” and “How?” deal with cause and pathogenesis, while “What?” is concerned with pathologic anatomy. In terms of energy and motion “What?” is static; “Why?” and “How?” are dynamic.

The arrangement of the book may require a word of explanation: The broad division of the subject into general and special pathology will probably evoke no controversy; nor will the further division of general pathology into disturbances of metabolism, inflammation,

and tumors. The approach by disturbances of metabolism rather than by the anatomic types of degeneration is a departure. It represents an attempt to give more emphasis to the physiologic and chemical aspects of general pathology.

In my experience the most desirable classification of disease is one based on cause; hence in the section on special pathology, diseases with similar causes have been grouped together. Those diseases of which the causes are unknown or obscure have been considered according to the organ or system in which they occur. My confidence that preventive medicine will play an important part in the future of medical science prompted the arrangement of the bacterial diseases according to the portal through which the bacterium enters the body and the source of the bacterium.

I have been guided in the selection of illustrations by certain principles: an illustration should expand the text; it should fix in the mind of the reader the important facts or observations about a disease; it should serve to correlate the pathologic with clinical observations; and it should stimulate the reader to further study. Illustrations are therefore not confined to gross and microscopic photographs, but radiographs, photographs of patients, reproductions of the frontispieces of classical monographs, pictures of the great men of medicine in the past, photographs from the field of paleopathology, and maps showing the distribution of disease, have been selected. Occasionally diagrams and drawings are advantageous, but so far as possible only actual photographic reproductions have been used.

References in a textbook serve two purposes: they indicate accessible works in which additional information on a subject can be found, and they call attention to the names of those who have made significant contributions to the sum of knowledge. The lists of references in this book have been compiled with a

full realization that there are many other contributions of equal value. So far as possible I have selected reports which answer these criteria: that the author has made many other contributions to the literature on the subject; that the journal is likely to be found in even small medical libraries; that the work is in English; that the bibliography is sufficient to point the way to future reading; and that the work has been published within the last few years. The number of citations varies from chapter to chapter, and is intended roughly to indicate the trend of present-day research, and conversely to point out chapters of medicine where investigation is most needed. The names of authors whose work is referred to are usu-

ally enclosed in parentheses in the text in order to familiarize the student with the names of men and women who are advancing the limits of knowledge in a certain field. The references are inserted for use and not for appearances, hence the preponderance in English is not a mark of provincialism, but a frank and practical acknowledgment that few Americans read any language except their own. Lists of journals are included at the end of some chapters to indicate sources of current literature. The date after the name of the journal is the year of first publication. If the publication of a journal has been discontinued a second date is included.

ROBERT A. MOORE

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which are known today by a proper name date from this period. Thus in France there were Corvisart, Laennec, Louis, and Cruveilhier; and in Britain, Carswell, Hodgkin, Bright, Addison, Cheyne, Stokes, Adams, Corrigan, and Graves.

At this time, pathology was not a separate science, but rather was an adjunct to clinical medicine. In a few isolated places, however, pathology was recognized as a distinct academic discipline, and the first professorship of pathology in the world was created at

While this progress in morbid anatomy and clinical correlation was taking place, the microscope had been invented; but for some reason it never occurred to a pathologist to use the microscope to study disease until the middle of the nineteenth century. In Berlin, under the influence of Johannes Müller, the cellular nature of all animal tissues had been proved by Schwann. Into this atmosphere came Rudolf Virchow, who studied under Müller, and who, on graduation, was appointed assistant prosector to the Charité. He



Fig. 1. Rudolf Virchow (1821–1902). (College of Physicians, Philadelphia.)

Strassburg in 1819. Lobstein was appointed to this chair. Soon thereafter in 1831, Carswell was made professor of pathology at the University College of London, and in 1836 Cruveilhier was appointed professor of pathology in the University of Paris.

Germanic Pathology. Although the French and the English brought pathology from the realm of speculation into the field of objective observation of diseased tissue, it remained for the Austrians and the Germans to complete the revolution. In Vienna Rokitansky, the supreme descriptive pathologist of all time, firmly established the structural basis of disease. As the result of his observations in the autopsy room, the work of Skoda, Semmelweis, and Billroth was made possible.

immediately applied the microscope and the cellular theory to pathology and, in 1846, the first edition of "Cellular Pathology" appeared. This book revolutionized the concepts of the nature of disease and the means which could and should be used to study it. Through his students, Virchow influenced the further development of pathology: through Cohnheim into the dynamic concepts of experimental pathology, through Klebs into the field of the bacterial causes of disease, through Hoppe-Seyler into the field of biochemistry, and through many students into the field of morbid anatomy.

American Pathology. The developments initiated by Virchow are of particular interest to Americans because American pathology

stems from this period, and has adopted the concepts and the methods of the Germanic school of pathology of the last half of the nineteenth century. It is true that there were a few isolated contributions to American pathology before this time, notably the textbook of Horner in 1829 and the classic work of Samuel Gross in 1839. It is also true that many of the great physicians and surgeons of Philadelphia, New York, and Boston brought back to America the ideas of the English and French schools of clinical pathology. But it

dynamic concepts of an integrated pathology, and it is along those lines that pathology has evolved in the United States.

The Present and Future. Pathologists are at one and the same time morbid anatomists, histopathologists, physiologic pathologists, and chemical pathologists. Pathology is a science which has no methods of its own. It applies to problems of disease the methods and the procedures of the anatomist, the chemist, and the physiologist. With this concept there is no limit to the field.



Fig. 2. William Henry Welch (1850–1934). (College of Physicians, Philadelphia.)

was not until the students of Virchow and his associates returned to America that pathology was recognized as a distinct science. The greatest of these were Welch, Councilman, Mallory, Prudden, Hektoen, Ophüls, and Warthin. William Henry Welch, a student of Cohnheim, in 1884 was appointed Professor of Pathology at Johns Hopkins University School of Medicine. Welch, more than anyone else, influenced American pathology and American medicine. His students occupy many of the important chairs of pathology in the United States, and there are few pathologists today who have not at one time studied under Welch or under one of his students. Welch and the others brought to America the

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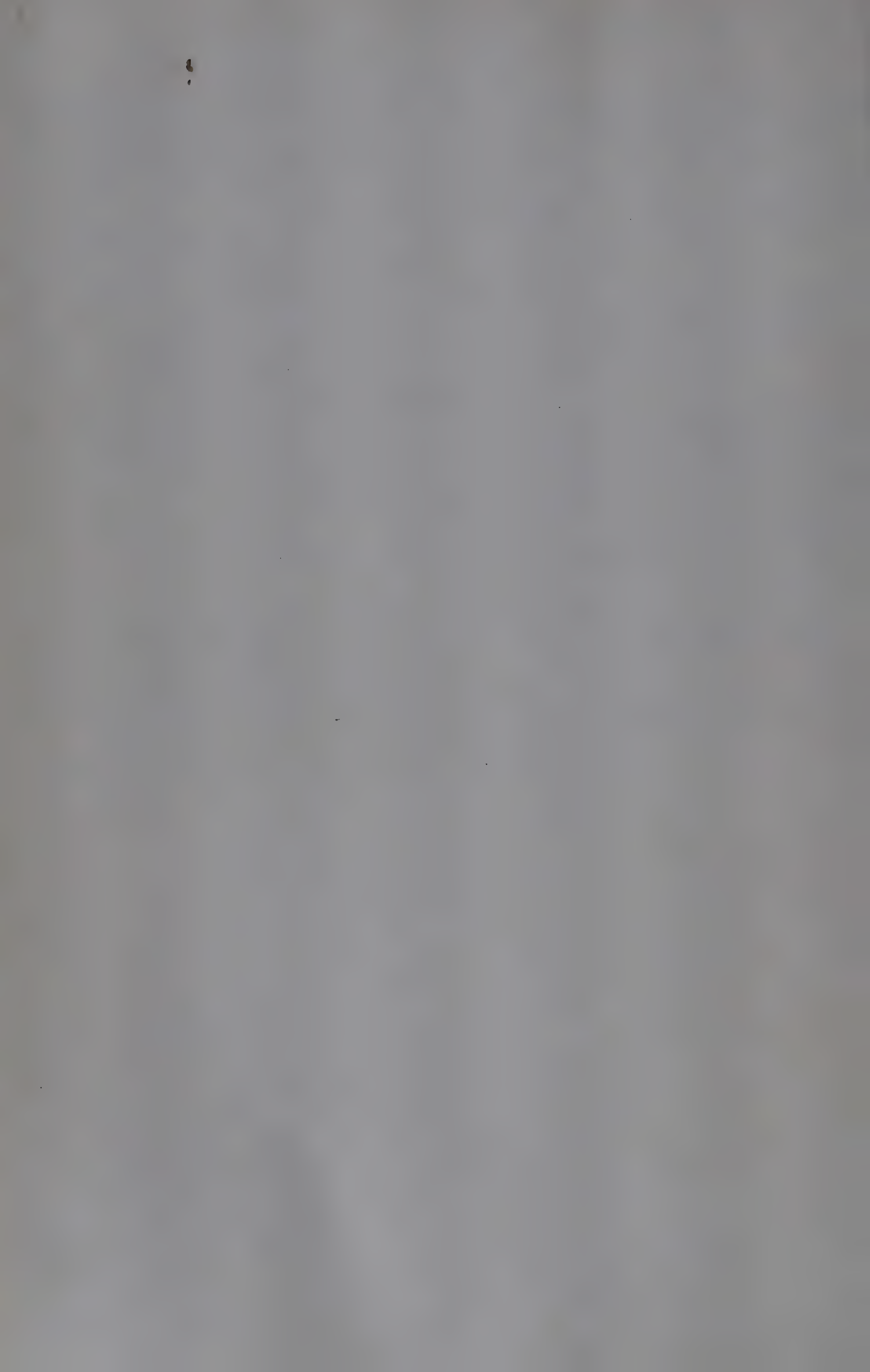
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PART I

GENERAL PATHOLOGY



II

Disturbances in the Metabolism of Proteins

The proteins are universal constituents of plant and animal tissue. Mulder, the Dutch chemist who in 1839 first suggested the term "protein," characterized it as "unquestionably the most important of all known substances in the organic kingdom." The role of proteins in life and metabolism is manifold: they are important in determining the osmotic relations between extracellular and intracellular fluids; many enzymes have the properties of proteins (pepsin); some hormones are either proteins or derived from proteins (thyroxine); and the substances associated with humoral resistance to disease are proteins.

Nature. Specificity. Amino acids are joined in peptide linkage to form polypeptides and proteins with molecular weights up to 7,000,000.

Each species of animal and plant, and frequently each cellular type or tissue, tends to construct a characteristic protein. It is probable that these differences are based on the quantitative and qualitative content and the special arrangement of the amino acids in the molecule, but this has not been proved. Present methods for the determination of the specificity of proteins are largely immunologic and depend on the phenomena of anaphylaxis, allergy, and the formation of antibodies.

Protein in the Body. Requirements. Sources. Nitrogen Balance. Nitrogenous substances are needed for general metabolism and for the building of new cells and tissues, as in growth, pregnancy, and lactation. If the dietary protein is adequate, the nitrogen of the diet (chiefly protein) is equal to the nitrogen of the excreta (chiefly in the urine). When the dietary nitrogen is in excess, a person is said to be in a positive nitrogen balance, whereas when the excreted nitrogen is in excess, the person is said to be in a negative nitrogen balance.

With an all vegetable diet the daily requirement for adults is about 2.9 gm. of nitrogen per square meter of body surface, and with a meat diet it is about 2.4 gm. of nitrogen (Hegsted, Tsongas, Abbott, and Stare).

In most human diets the protein is derived from animal products (meats, eggs, fish, and milk), cereal, grains, legumes, and nuts. In the United States, animal protein makes up about 50 per cent. of the total (Lewis).

Dynamic Equilibrium. The protein of the animal body may be considered as a single pool and may flow from cell to plasma or the reverse, depending upon the conditions of the moment (Whipple and Madden). The largest pool of stored protein and the chief center of manufacture is the liver.

Plasma Proteins. The normal plasma protein value for white adults is 7.19 gm., with 4.65 gm. of albumin and 2.59 gm. of globulin (Milam).

Fractionation of the plasma proteins has yielded many products useful in treatment, such as globulin for immunization and fibrin foam for hemostasis (Cohn, Oncley, Strong, Hughes, and Armstrong Cohn).

Demonstration of Protein in Tissue. Most chemicals used for the fixation of tissue are protein precipitants and, in the subsequent treatment with aqueous and organic solutions, most carbohydrate and lipid are removed. Hence the greater part of the material seen in sections of tissue is protein. The density of the cytoplasm is a rough index of the concentration of protein. Basophilism of the cytoplasm indicates the presence of nucleoproteins, particularly ribonucleic acid (Opie). Some of the specific tests for the identification of protein may be used histochemically, such as the biuret and xanthoproteic reactions.

Effects of a Deficiency of Protein

A deficiency of protein may be related to decreased intake as in starvation, defective absorption as in disease of the intestines, increased loss as in certain renal diseases and after injury, or decreased synthesis as in some diseases of the liver. Changes in the plasma proteins chiefly take the form of a decrease in albumin (Muntwyler).

Within a few hours after the loss of from 20 to 30 gm. of plasma protein by hemorrhage the volume of the blood is restored by the withdrawal of fluid from the tissues, and within six to twelve hours the protein concen-

passage of fluid into the tissues. When the level of plasma protein reaches about 4 gm. per 100 cc., the differential between osmotic pressure and blood pressure is sufficiently low that fluid passes out of the blood vessels. This fluid contains only a small amount of protein, and there is a direct correlation between specific gravity and the concentration of protein (Paddock). This phenomenon of nutritional edema is common during war time (Chen).

Anatomic Changes. In man it is difficult to separate the changes caused by a deficiency of protein from those resulting from a grossly deficient diet, leading to starvation. In starvation there is a deficiency not only of protein

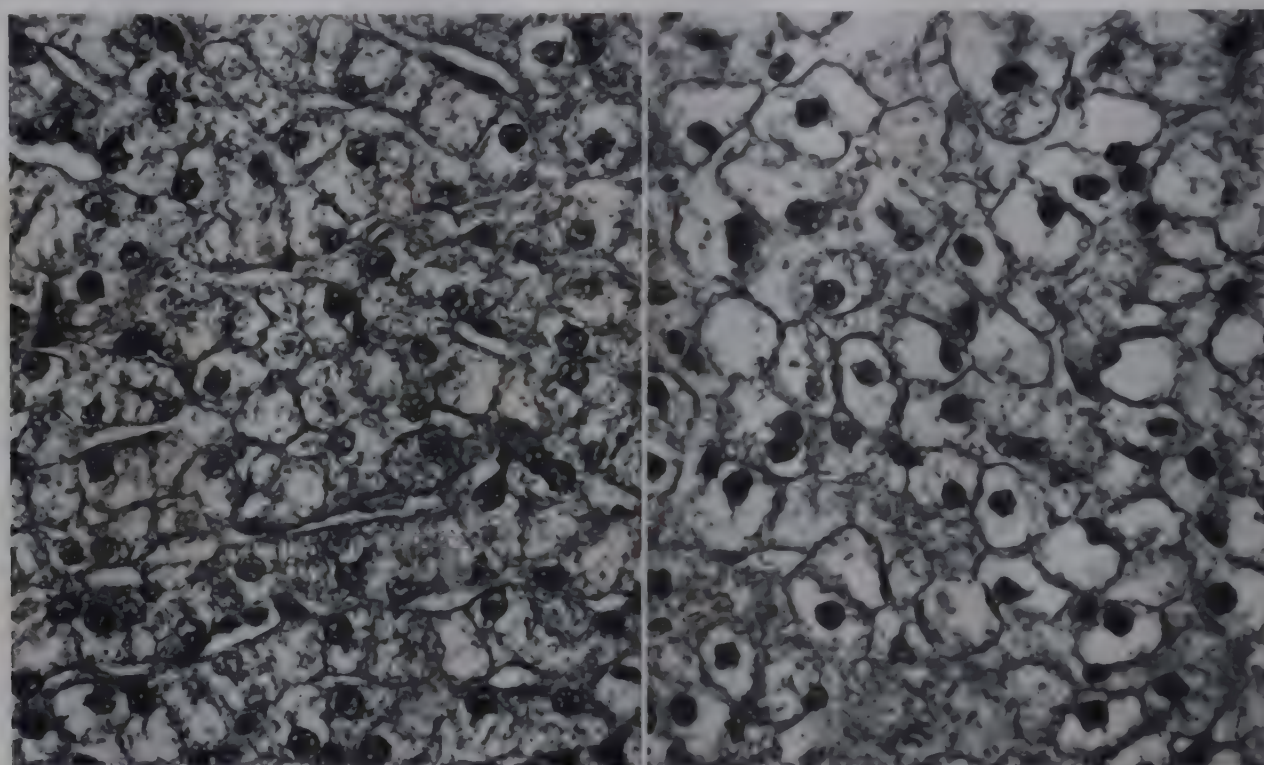


Fig. 3. Two stages in the depletion of protein from hepatic cells. (Tissue by courtesy of Dr. Robert Elman.)

tration of the blood has been restored to normal. In chronic depletion there is a maximum regenerative capacity, which in the dog is in excess of 70 gm. of plasma protein per week under optimum conditions (Whipple and Madden).

Hypoproteinemia. Nutritional Edema. Maintenance of the dynamics of the circulation is dependent on the blood pressure and the osmotic pressure of the plasma proteins. Fluid is held within the blood vessels by the osmotic pressure against the force of the blood pressure, which tends to drive it into the tissues. Perfect maintenance of the balance between the fluid within the blood vessels and the extravascular fluid thus depends on the maintenance of the level of the plasma proteins at about 7 gm. per 100 cc. of plasma. Any decrease of protein tends toward the

but of carbohydrates, fats, and vitamins. As the anatomic changes in starvation are more concerned with the metabolism of fats, this subject will be discussed in detail in the chapter on fats (Chapter V, p. 39).

In animals in the laboratory specific histologic changes result from the administration of a diet which is deficient only in proteins. In dogs, after periods of two to three weeks, the liver is smaller than normal, grayish brown, and soft. The hepatic cells, especially those about the hepatic vein, are enlarged, and the cytoplasmic substance is not recognizable. The cell wall is thick and prominent, and in the center or at the side of a clear space there is a relatively small hyperchromatic nucleus (Elman, Smith, and Sachar).

Effect on Resistance to Disease and Toxic Agents. It is a well known observation that

the animal organism depleted of protein is more susceptible to infection (Cannon) and to toxic agents (Nutrition Reviews). The mechanism of this is not fully understood but in the former it would appear to be an impairment of capacity to fabricate antibody gamma globulin (Cannon, Chase, and Wissler); and in the latter an interrelation between sulfhydryl groups and the liver.

Effect on the Healing of Wounds and the Restoration of Tissue. A protein deficient diet also influences the rate of regeneration of hepatic tissue following partial hepatectomy (Rous and McMaster). The hypertrophy of a remaining kidney, adrenal, or ovary may be delayed (Addis and Lew). The healing of wounds progresses more slowly in dogs fed a diet deficient in protein than in normal dogs (Thompson, Ravdin, and Frank).

Post-traumatic Negative Nitrogen Balance. Following injury or surgical operation there is usually a negative nitrogen balance due to decreased intake, increased catabolism of protein, and loss of plasma protein (Elman; Madden and Clay). The condition may be corrected by an increased intake of protein (Elman).

EFFECTS OF A DEFICIENCY OF SPECIFIC AMINO ACIDS

Rose has demonstrated that ten amino acids are required for the normal growth of the white rat. These are lysine, tryptophane, histidine, phenylalanine, leucine, isoleucine, threonine, methionine, valine, and arginine. Small quantities of arginine can be synthesized by the animal organism, but not sufficient to maintain growth. Observations on the dog and in man indicate that these same ten acids will maintain nitrogen balance and serve for synthesis of plasma protein (Madden and Whipple).

A beginning has been made in the study of each amino acid separately. Lack of lysine in man leads to nausea, dizziness, hypersensitivity to sound, and increased excretion of non-ketonic organic acids (Albanese, Holt, Frankston, Kajdi, Brumbach, and Wangerin). A deficiency of arginine in man is associated with aspermia (Holt, Albanese, Shettles, Kajdi, and Wangerin). A histidine deficient diet in man results in weight loss and increased excretion of an indican-like substance, but no negative nitrogen balance (Albanese,

Holt, Frankston, and Irby). In the rat, deficiency of tryptophane causes changes in the teeth, eyes, and testes (Albanese, Randall, and Holt), but in man there are no clinical alterations (Holt, Albanese, Frankston, and Irby).

A deficiency of cystine in mice retards the occurrence of both spontaneous and of induced tumors (Nutrition Reviews).

Although there is no evidence on the results of a deficiency of glutamic acid, there is clear evidence that additional amounts in a supposedly normal diet will increase the intellectual ability of both animals and man.

Effects of an Excess of Protein

So far as is known the ingestion of an excess of protein has little deleterious effect upon the animal organism other than to produce a certain degree of obesity. This phase of the subject will be discussed in the chapter on disturbances in the metabolism of fats (Chapter V). Rats on a diet containing 10 per cent of *l*-tyrosine show purulent keratitis, and swelling and redness of the feet and legs (Hueper and Martin), and both degenerative and fibrotic lesions in the viscera. On the other hand, studies of men who lived for a year on a diet of meat failed to show any harmful effects (McClellan and Du Bois).

Hyperproteinemia. A value of the plasma proteins above 8.5 gm. per 100 cc. is pathologic and is seen in hepatic disorders, venereal lymphopathy, certain acute and chronic infections, and in extreme dehydration. There are no demonstrable associated histologic lesions (Cardon, Atlas, Brunner, Aron, and Teitelman).

EFFECTS OF AN EXCESS OF SPECIFIC AMINO ACIDS

Aside from indefinite changes in animals there is only one very clear effect of an excess of a specific amino acid—cystine.

Experiments in rats and mice indicate that the normal state of the liver and kidneys depends on the dietary balance between cystine on the one hand, and choline and methionine on the other hand. With high cystine and low choline there is fatty metamorphosis of the liver and, in young animals, there is also a hemorrhagic lesion of the kidneys (Griffith and Wade).

The direct application of this knowledge to

disease in man is not clear, but choline is useful in the treatment of patients with cirrhosis of the liver.

Disturbances in the State of Intracellular Proteins

Under normal conditions the protein in the cytoplasm of cells is in an evenly distributed, homogeneous, colloidal state. In some pathologic conditions the even distribution, the homogeneity, or the colloidal state may be

cloudy and granular, and the nuclei indistinct. The granules in the cytoplasm are soluble in dilute acetic acid and alkalis and give the xanthoproteic reaction, indicating that they are proteins. Virchow was impressed with the cloudy appearance of the cell, and suggested the term "cloudy swelling." Others, with a chemical turn of mind, have proposed the name "albuminous degeneration," while still others, with an anatomic approach, have adopted the designation "parenchymatous degeneration." Until we know more about the

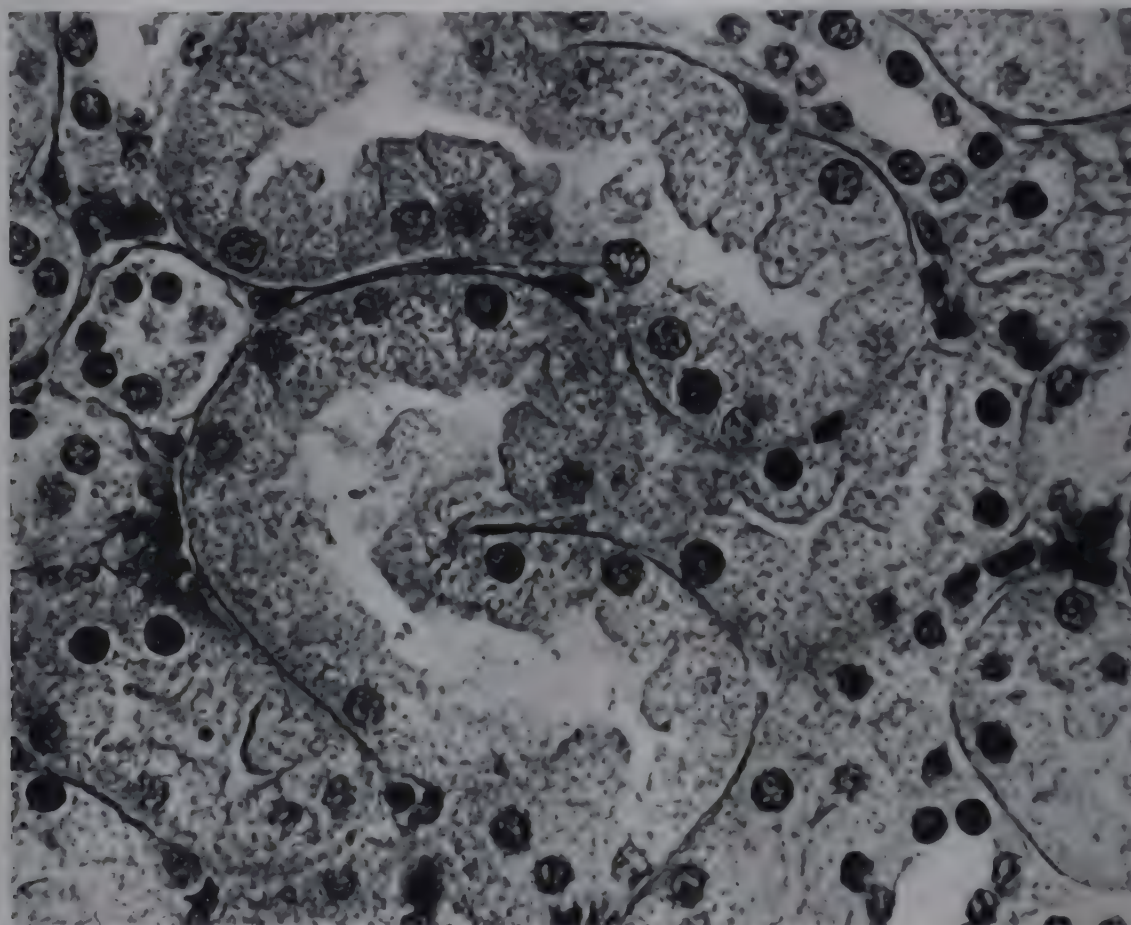


Fig. 4. Cloudy swelling of the renal epithelium. Note the granularity of the cytoplasm and variation in the chromatism of the nuclei.

disturbed. These lesions are classified as degenerations and include cloudy swelling, hydropic degeneration, hyaline droplet formation, and Zenker's hyaline degeneration.

Cloudy Swelling. In many pathologic states the parenchymatous viscera are enlarged and turgid, and do not have the transparency of normal tissue. In fact the tissue appears as though it had been dipped in boiling water—parboiled. When sectioned, the parenchyma bulges from beneath the capsule, and the substance of the organ is gray, semi-opaque, soft, and friable, and the architecture is partially obscured. If a small piece of the organ is crushed between a slide and a cover slip, or if an unfixed frozen section is prepared, the cells are observed to be enlarged, the cytoplasm

exact physical and chemical nature of the condition it seems best to use the original term "cloudy swelling."

In fixed and stained sections the cells are observed to be enlarged 25 to 100 per cent above normal, and the cytoplasm is increased to a greater extent than is the nucleus, although both participate in the process (Davidman and Dolley). The cytoplasm is finely or coarsely granular (depending on the type of fixation and other technical procedures), and the nucleus may show a slight degree of hyperchromatism or hypochromatism. There is no histologic evidence that the granules are derived from the mitochondria. Early the cell walls are conspicuous, and late they may become indistinct and a part of the cytoplasm

may be lost. Droplets of "myelin" and fat in the cells, described by some investigators, are probably expressions of necrosis or fatty degeneration.

The description given in preceding paragraphs is that of a typical example of cloudy swelling. Unfortunately there are many variations and inconsistencies. A liver or kidney may show all of the gross but none of the microscopic characteristics of cloudy swelling; or the reverse may be true. It is possible that the gross appearance is that not only of cloudy swelling, but also of fatty degeneration and edema (Bell). Further study is needed in order to explain the apparent paradoxes.

Chemical Changes. Chemical study of an organ showing either the gross or microscopic changes of cloudy swelling reveals increase in water content, decrease of specific gravity, increase of coagulable protein, and more rapid autolysis.

Swelling of Cells in Vitro. Since the swelling of cells is the most prominent feature of cloudy swelling, many investigators have hoped to secure information from studies in vitro. Some of the best of these are those of Lucké and McCutcheon, who observed the changes in the volume of the eggs of the sea urchin in response to different agents. They have shown that the rate of diffusion of water into the eggs follows the usual formula of chemical reactions of the first order. The temperature coefficient of the rate of diffusion is high—2.4 per 10° C.—and is fairly uniform over a wide range. These two facts indicate, respectively, that the passage of water into the cell is a complex process, involving chemical reactions rather than simple diffusion, and that changes in viscosity have little influence. Agents such as hydrochloric acid, salicylic acid, heat, and ether produce irreversible gelation of the cytoplasm. In general, gelation is preceded by swelling of the cell. Further study is necessary to determine whether or not these observations are applicable to mammalian cells.

Occurrence of Cloudy Swelling. Some degree of cloudy swelling is observed in the liver, kidney, heart, and other parenchymal organs and cells of most persons who die of infectious disease. It is assumed that the diffusible toxins of the bacteria injure the cells. A similar explanation is given for the occurrence of cloudy swelling in association with extensive thermal

burns, but the observation of cloudy swelling in inanition is less easily explained. Experimental cloudy swelling is frequently observed in association with anoxia, following the injection of toxic substances and chemicals, and in the remaining kidney after unilateral nephrectomy.

Nature of Cloudy Swelling. Many theories have been proposed to explain cloudy swelling, but none has been fully accepted.

CHANGES IN PH AND ANOXIA. Fischer postulated that the basic change is an increase of the intracellular hydrogen ion concentration, which alters some proteins (hydrophilic) so that they take up water and swell, and other proteins (hydrophobic) so that they precipitate or aggregate. Opposed to this view is the lack of evidence that the pH ever changes enough to bring about the observed degree of swelling (Henderson and Cohn). There is the further objection that swelling of fish eggs induced by acids is irreversible and involves coagulation of the protein and death of the cell (Lucké and McCutcheon). The appearance of cloudy swelling in organs subjected to anoxia is consistent with an assumed accumulation of acidic substances in the cell.

CHANGES IN THE METABOLISM OF PROTEINS. Virchow looked upon the accumulation of albuminous granules as overnutrition of the cell, and assumed that some slight injury impairs the ability of the cytoplasm to assimilate protein brought to it by the blood. Somewhat similar is the view taken by those who are impressed with the occurrence of cloudy swelling with overwork, as in a single kidney after unilateral nephrectomy. On the other hand Connheim believed that the granules are derived from the preexisting protein of the cell and are the product of some process analogous to coagulation. Precise physical and chemical studies of experimentally produced cloudy swelling would determine whether there is defective synthesis of protein or defective hydrolysis of protein or both in cloudy swelling. The passage of water into the cell implies that there is an increase of the osmotic forces within the cell as opposed to those of the extracellular fluids. Whether this is caused by accumulation of salts or by the split products of protein has not been proved, but the rapid progress of autolysis in cells with cloudy swelling suggests the existence of a preceding alteration in the breakdown of protein. On the

other hand the increase of coagulable protein in tissue extracts indicates an accumulation of protein caused either by failure of complete synthesis or by incomplete oxidation of the initial hydrolytic products. Since the semipermeable character of the cell membrane is not lost until death, it is logical to believe that water would diffuse into cells more rapidly than larger molecules would diffuse out into the lymph and blood.

EFFECT OF FEVER. The appearance of cloudy swelling with fever has led to the sug-

ance is not characteristic. Microscopically, vacuoles appear in the cytoplasm which do not give the staining reactions, nor do they have the appearance of fat, glycogen, or other substances that cause vacuolation of cells. The nuclei are preserved, and the cell wall is distinct, indicating that the process is reversible.

Hyaline Droplets. In many epithelial cells, notably those of the liver and kidney, small and large, spherical, homogeneous, deeply acidophilic droplets may be observed in the cytoplasm in association with other degener-

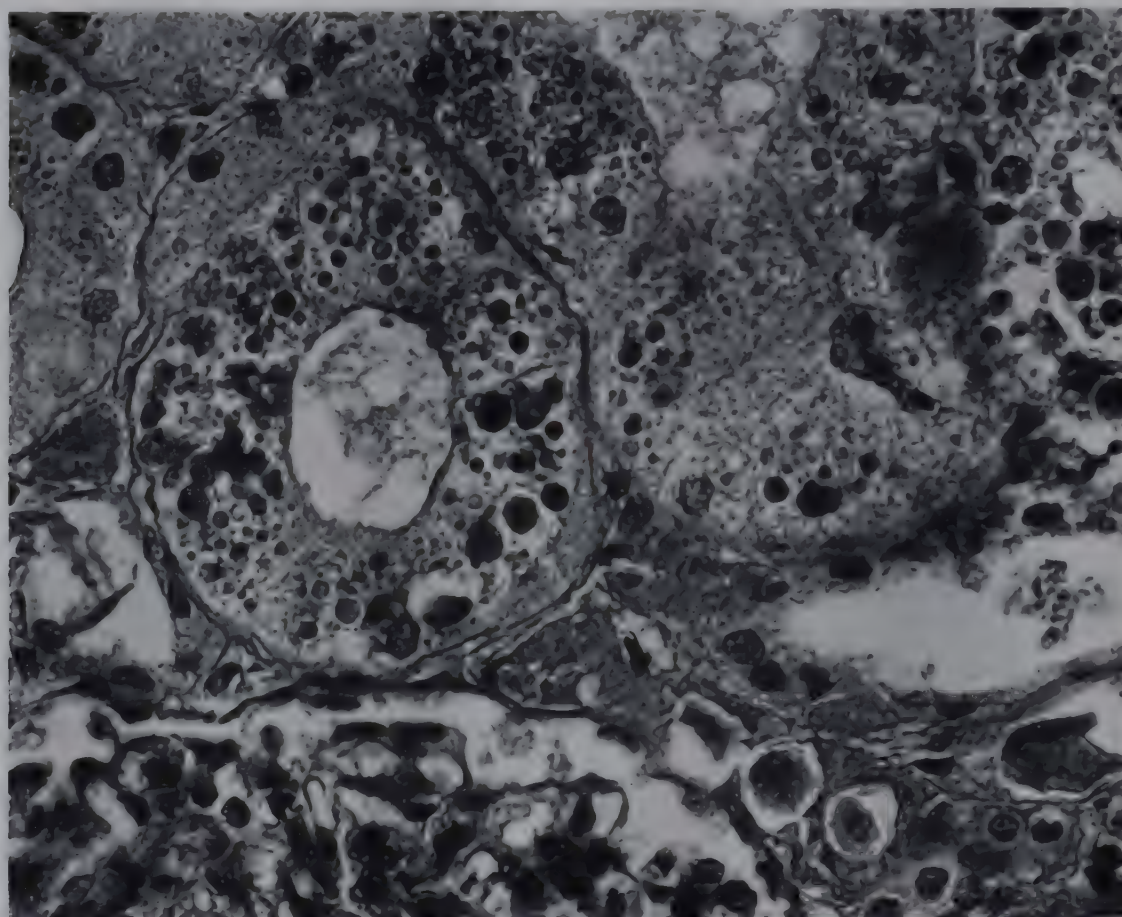


Fig. 5. Hyaline droplets in the renal epithelium.

gestion that the granules are nothing more than heat-precipitated proteins. Their solubility in acetic acid is sufficient evidence to reject this, since heat-precipitated protein is not soluble in dilute acid.

SUMMARY. From the factual data available it is evident that cloudy swelling does not represent a single pathogenetic entity but rather the anatomic end result of many different physical and chemical alterations in cells. Future study must elucidate the exact alterations in the metabolism of cells induced by the various causal agents.

Hydropic Degeneration. Hydropic degeneration probably is a variant of cloudy swelling in which the increased intracellular water accumulates in a vacuole rather than diffusely throughout the cytoplasm. The gross appear-

ative changes. There is no consistent change in the macroscopic appearance of the organ.

Hyaline Droplets in the Renal Epithelium. Typically the droplets are located in the cells of the proximal convoluted tubules. They vary in size, are spherical, and are deeply acidophilic (Fig. 5). The cytoplasm of the involved cells may be relatively normal or may show the changes of cloudy swelling and fatty degeneration. The nuclei are normal, and the cell walls are distinct.

In urodeles with open and closed nephrons it can be readily demonstrated that hyaline droplet formation is a means of storage of protein absorbed from the lumen of the tubules. Although there is no direct proof, these observations strongly suggest that the same lesion in man is the result of storage of pro-

tein excreted through a damaged glomerular membrane (Smetana and Johnson).

Hyaline Droplets in Hepatic Cells. In cirrhosis of the liver in patients who have consumed large amounts of alcoholic beverages the hepatic cells contain small hyaline droplets. With progress of the disease the droplets enlarge and fuse to form a coarse reticulum. Although it has been claimed that these droplets are stored protein, the general belief is that they are a manifestation of a degenerative change in the cytoplasm (Mallory).

acid from overproduction, underelimination, or underoxidation (Wells) (Fig. 6).

Disturbances in the Colloidal State of Extracellular Proteins

The extracellular proteins are normally arranged in a definite pattern, as in the matrix of cartilage, and the fibrillar material of collagen, reticulum, and osteoid. The mechanism of formation of one of these—collagen—is known. If the animal organism is deprived of

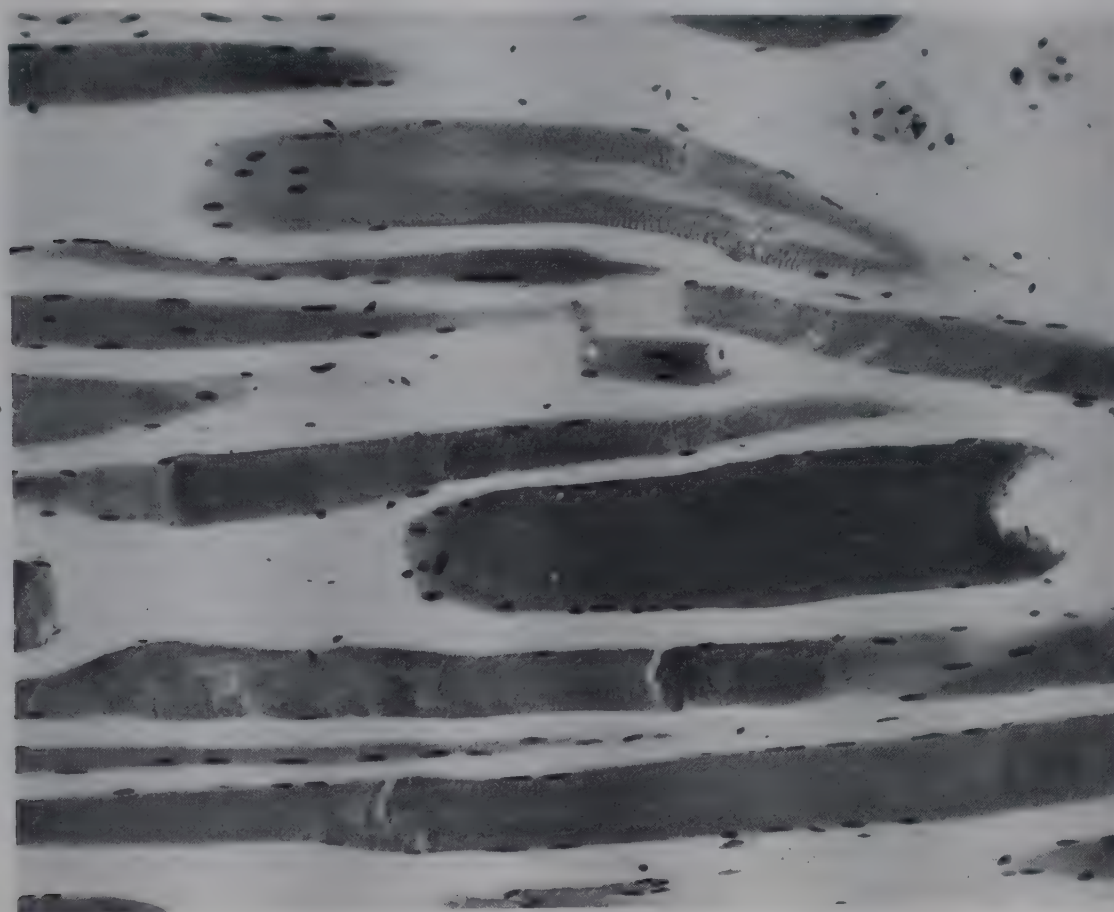


Fig. 6. Zenker's hyaline degeneration of skeletal muscle. From a child with acute streptococcal septicemia. (Tissue by courtesy of Dr. Jacob Werne.)

Zenker's Hyaline Degeneration of Skeletal Muscle. In many infectious diseases and in anaphylactic shock the skeletal muscles are pale, opaque, and waxy in appearance. The cytoplasm in a part or all of a fiber is converted into a dense, homogeneous, swollen, deeply acidophilic mass, and the normal striations are completely lost. Occasionally in severe examples the muscle ruptures and there is secondary hemorrhage. These changes are more prominent in the rectus abdominis muscle and in the diaphragm. Functional inability or paralysis of the diaphragm induced by degenerative change may play a role in causing death in respiratory infection and in anaphylaxis. The most logical explanation of the condition is an excessive accumulation of lactic

vitamin C, the fibroblasts elaborate a peculiar viscid intercellular substance devoid of fibrils and possessing little tensile strength. The administration of vitamin C results in precipitation of collagenic fibrils from the homogeneous matrix.

Under pathologic conditions the separate fibrils of collagenous connective tissue may fuse to form a firm, dense, homogeneous mass, known as "connective tissue" or "von Recklinghausen's hyalin." This change probably represents a physical rather than a chemical alteration, since the staining properties of the collagen are retained. Connective tissue hyalin is seen under conditions in which there is an excessive formation of dense fibrous tissue, as in scars, in fibrous thickening of the serous

membranes, in chronic inflammations, and in some mesodermal tumors. It appears grossly as a bluish gray, translucent, homogeneous tissue; and as seen microscopically is homogeneous, acidophilic, and relatively acellular. Small foci of calcification and ossification are not infrequently observed. The more frequently encountered examples are in the thickened pleura of chronic empyema, in thickening of the splenic capsule (Fig. 7), in the fibrous healing of tuberculous lesions, in

literated and the entire cut surface has a glassy appearance. If it is deposited focally, the regions with amyloid appear translucent and transmit the color of the underlying tissue. The liver, spleen, and kidneys are most frequently involved, but all organs and tissues may contain infiltrations.

The *kidneys* are slightly to moderately enlarged and average about 200 gm. The capsule is not adherent, and the surface is smooth. On the cut section little distinction between

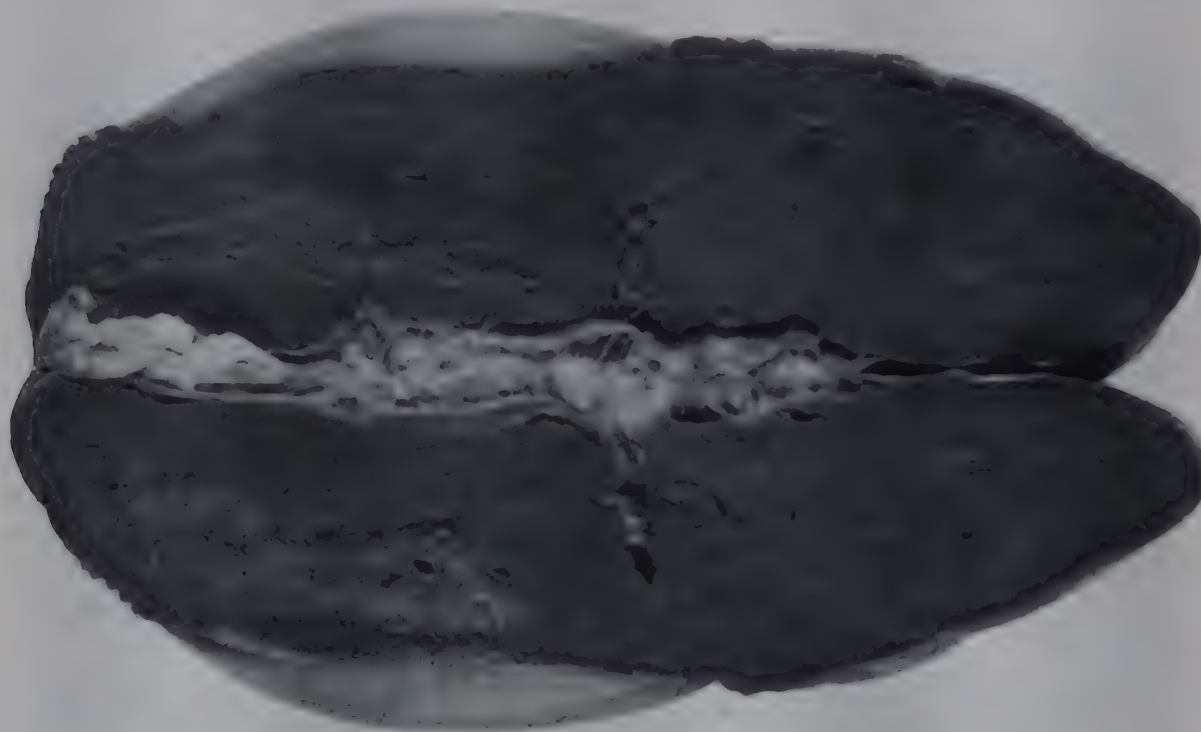


Fig. 7. Thickening and hyalinization of the splenic capsule. (Specimen from autopsy No. 915 by Dr. Eugene L. Opie of Base Hospital No. 21, Rouen, France, 1917-1918.)

large leiomyomas of the uterus, and in the corpora albicantia of the ovary.

Endogenous Formation and Deposit of Abnormal Proteins

Under all normal and most pathologic conditions the proteins of an animal organism are characteristic, and are immunologically and chemically similar. In a few pathologic conditions an abnormal protein is formed, and deposit of it in the tissues interferes with function, causing typical and at times diagnostic clinical signs. The substances known as amyloid and as Bence Jones protein are the most important.

AMYLOID

Pathologic Anatomy. In amyloidosis the organ is slightly to moderately enlarged, firm, waxy, and relatively bloodless. If the amyloid is deposited diffusely, the architecture is ob-

literated and the cortex and medulla is discernible, and the glomeruli may be visible as small, elevated, gray, shining dots. The *liver* is enlarged, firm, and pale. If the deposit is slight to moderate, an interlacing network of bluish gray, translucent lines is seen through the capsule and on the cut surface. With excessive deposit, the architecture is completely obliterated and the cut surface has a uniform glassy appearance. Two types of amyloidosis of the *spleen* are recognized: in one the amyloid is deposited in the malpighian bodies, and they appear grossly as bluish red, translucent bodies in contrast with the darker red pulp; in the second type there is diffuse infiltration, and the organ is enlarged, firm, and waxy or glassy in appearance.

Amyloid is characteristically deposited beneath the endothelium of capillaries and in the walls of the arterioles. In the kidney it is found within the glomerular tufts, in the afferent and efferent arterioles, and in the arteri-

olae rectae (Fig. 8, *A*). In the liver the homogeneous, slightly acidophilic material is deposited between the endothelium of the sinusoids and the basement membrane, separating them from the cords of hepatic cells (Fig. 8, *B*). In the spleen it is in the walls of the central arterioles, beneath the endothelium of the capillaries of the white pulp, and in the cords of the red pulp.

Amyloid is to be recognized as a palely acidophilic, homogeneous, extracellular substance, with certain characteristic staining properties. If iodine is poured on the cut sur-

berculosis, pyogenic infections, or syphilis, in which there is extensive destruction of tissue. It is found in about 40 per cent of all patients with chronic pulmonary tuberculosis and in a somewhat higher percentage of those with tuberculosis of the bones and of the parenchymatous viscera (Pearlman).

Primary Amyloidosis. In contrast, primary amyloidosis involves mesodermal derivatives, and the condition is not associated with any other disease. Localized and systemic forms are recognized. In the local form one organ is extensively involved and there are insig-

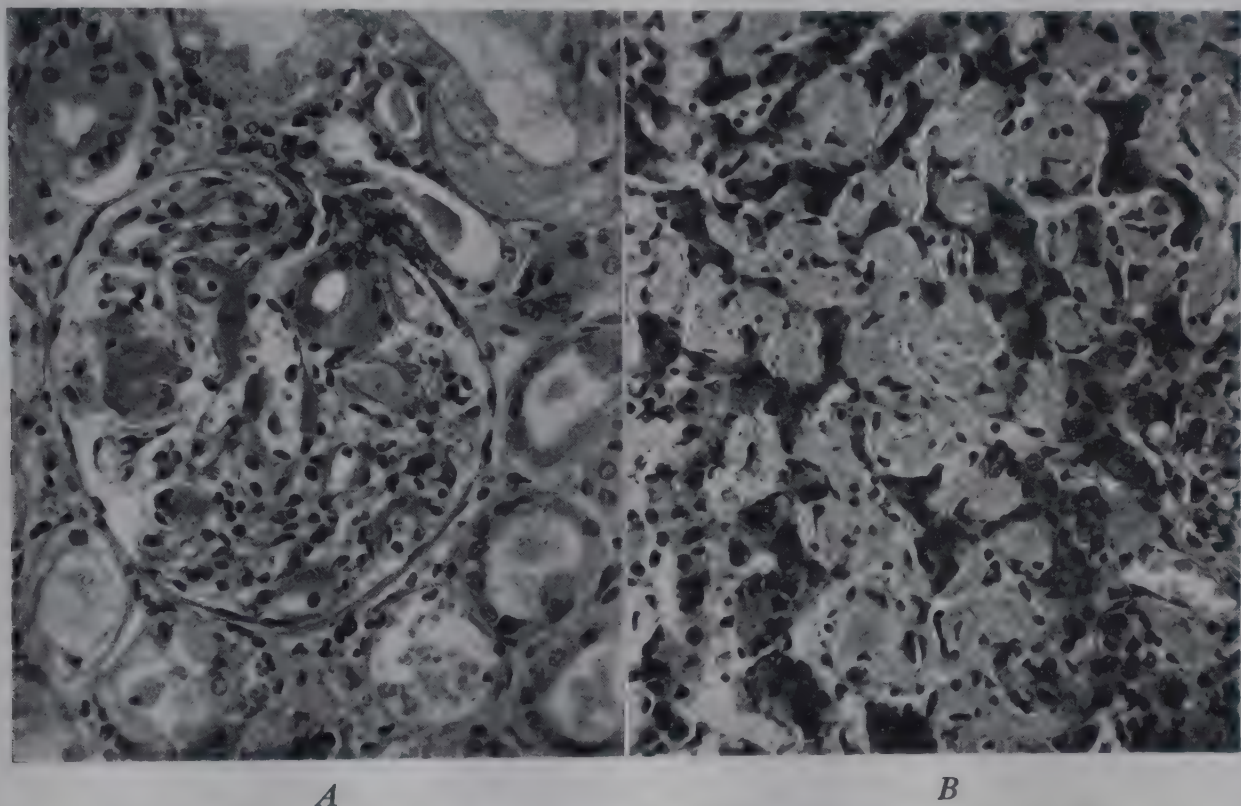


Fig. 8. *A*, Deposit of amyloid in walls of glomerular capillaries. *B*, Amyloidosis of liver. Note the separation and atrophy of the hepatic cells.

face of an organ with amyloidosis, the deposits are stained a dark brown, changing to blue on addition of sulfuric acid. For microscopic study the metachromatic dyes (gentian violet, crystal violet) are most useful, especially with frozen sections. The amyloid takes up the red, while the tissue generally stains blue. Congo red is also a satisfactory stain for either paraffin or frozen sections.

Types of Amyloidosis. Amyloid disease may be divided into four groups: (1) secondary amyloidosis, (2) primary amyloidosis, (3) amyloid associated with multiple myeloma, and (4) tumor-forming amyloidosis.

Secondary Amyloidosis. In secondary amyloidosis the deposits are in the parenchymatous organs, chiefly liver, spleen, and kidneys, and the condition is almost always associated with some chronic disease such as tu-

nificant deposits in the other tissues. The most frequent sites are tongue, intestine, skin, myocardium, lungs, and skeletal muscle. In many instances the amyloid in the primary type stains atypically.

Amyloidosis Associated with Multiple Myeloma. In about 7 per cent of all examples of multiple myeloma there is an associated amyloidosis of mesodermal tissue. The reason for this association is not clear, but it has been suggested that amyloid and Bence Jones protein (see p. 16) are chemically related, and that the latter may serve as the mother substance of the former (Tarr and Ferris).

Tumor-Forming Amyloidosis. Occasionally amyloid is deposited in tumor-like nodules in the subcutaneous tissues or in the mucous membranes.

Pathogenesis and Causal Factors. Despite

elaborate study the mechanism of formation of amyloid is still unknown. There are two possibilities: that it is formed locally as an abnormal product of fibroblasts (Warren), or that it or a mother substance is elaborated throughout the body and precipitated out in the organ or tissue where it is found. The second theory explains more objective facts. Electrophoretic studies of the plasma proteins in patients with amyloidosis would be most helpful in an elucidation of this problem. The mass of evidence indicates that amyloidosis is the product of a reaction between some component of the plasma globulin and certain fixed tissue elements.

Chemical Nature. The word "amyloid" was coined by Virchow because of his belief that it was a starch-like substance. It has since been proved that it is a protein, but little progress beyond this has been made. Hass, Huntington, and Krumdieck were able to isolate the relatively pure proteins of amyloid by successive extraction at pH 7, 10, and 11; the protein of amyloid is in the last fraction. Whether or not amyloid contains chondroitin sulfuric acid is still unsettled.

Clinical Significance. In secondary amyloidosis about 60 per cent of the patients are dead in six months and 80 per cent within one year after the diagnosis is established. In most instances death is not caused by the amyloidosis, but the short survival period is a reflection of the severity of the associated tuberculosis or osteomyelitis (Pearlman). In primary amyloidosis the average survival is two and one-half years after clinical signs appear.

Amyloid Nephrosis. In all cases of amyloidosis there is albuminuria, but in only about 30 per cent are there other evidences of renal insufficiency such as retention of nonprotein nitrogen and signs of uremia. Hypertension with amyloid nephrosis is seen in about 5 to 10 per cent of patients. The causes of these functional alterations are probably the deposit of amyloid in the glomeruli, blockage of the tubules by casts, and deposits in the basement membrane of the tubules and peritubular capillaries (Auerbach and Stemmerman).

Amyloidosis of the Liver. Infiltration of the liver produces little functional change. Slight lowering of the plasma proteins (independent of albuminuria), slight diminution of glucose tolerance, and a slight macrocytic anemia

have been reported (Tiber, Pearlman, and Cohen).

Amyloidosis of Other Organs. Infiltration of the adrenals may result in functional insufficiency (Stemmerman and Auerbach), of the myocardium or valves in signs and symptoms of cardiac failure (Lindsay), of the uterus in amenorrhea (Reimann, Koucky, and Eklund), of the intestine in obstruction, constipation, or diarrhea, of the skeletal muscles in weakness and enlargement similar to that of myotonia, and of the tongue in macroglossia with dysphonia and dysphagia. Amyloidosis of the thyroid is not associated with hypothyroidism (Walker). Lesions of the skin appear as papules or plaque-like tumors, with or without ulceration. Amyloid tumors of hollow viscera, such as the larynx, may cause obstruction.

The apparent chemical union between amyloid and Congo red is utilized for clinical diagnosis by determining the rate of removal of the dye from blood. Both false positive and false negative results are occasionally secured (Stemmerman and Auerbach).

Resorption. An important consideration in prognosis is whether or not amyloid is resorbed if once deposited. Do children with severe osteomyelitis of the tibia and clinical signs pointing to amyloidosis recover if the leg is amputated? There are a few studies in man that suggest that amyloid is slowly resorbed if the associated lesion is removed (Métraux).

Experimental Amyloidosis. Deposit of amyloid in animals has been reported after injection of living or dead bacteria and of sodium caseinate (nutrose), after hyperimmunization of horses, and after feeding of excessive amounts of cheese and other proteins to mice. In all of these conditions there is a hyperglobulinemia. Amyloidosis occurs in experimental tuberculosis of rabbits.

BENCE JONES PROTEIN

The term "Bence Jones protein" refers to an ill defined group of proteins having a molecular weight of approximately 3700, and the characteristic property of precipitating out of solution when warmed to 45° to 58°C. and of redissolving completely or partially on boiling. It is found in the plasma and urine of about 70 per cent of patients with multiple

myeloma and occasionally in association with leukemia, Hodgkin's disease, and lymphosarcoma.

Pathologic Anatomy. The only morphologic evidence of the existence of Bence Jones protein is in the kidney, where the excreted protein forms dense casts in the renal tubules. The resultant obstruction leads to tubular atrophy and loss of renal substance to the point of functional insufficiency. Foreign body giant cells may form about the casts (Bell). Similar lesions can be produced in mice by the injection of the Bence Jones protein (MacMahon and Magnus-Levy).

Origin of Protein. The most persuasive theory is that the tumor cells elaborate the abnormal protein, but the huge amounts formed suggest that there may be a generalized defect of protein metabolism. Immunologically the Bence Jones proteins differ among themselves and are distinct from normal plasma proteins (Bayne-Jones and Wilson). They contain sulfur and a high proportion of aromatic amino acids (Lüscher). In most patients with Bence Jones proteinemia there is an associated hyperglobulinemia of normal gamma globulin (Moore, Kabat, and Gutman).

Disturbances in the Metabolism of Specific Amino Acids

During the metabolism of proteins within the cell, free amino acid is eventually hydrolyzed to form simpler substances. The hydrolysis of each amino acid is carried out in a different way, and in a few instances defects in this hydrolysis, usually hereditary, have been detected in man. So far as is known no anatomic lesions are associated with these physiologic defects.

Phenylketonuria. In a certain number of mentally defective persons a large amount of phenylpyruvic acid is excreted in the urine, increased by the ingestion of phenylalanine. The defect seems to be an inability to oxidize the ketonic acid derived from the primary oxidation of phenylalanine (Jervis). Avitaminosis C in premature infants leads to phenylketonuria (Levine, Gordon, and Marples).

Tyrosinuria. In this condition tyrosine is oxidized to *p*-hydroxyphenylpyruvic acid. This acid in the enol form is excreted in the urine—about 1.6 gm. per day. The feeding of tyrosine increases the urinary excretion. An-

other derivative of tyrosine, homogentisic acid, is fully oxidized by these patients (Medes).

Histidinuria. The normal human being excretes only minimal amounts of histidine in the urine. During pregnancy there is a definite increase, so that from 1 to 2 gm. may be found in the urine in a day, and this may be increased by the ingestion of a protein rich diet (Kapeller-Adler and Schiller). In eclampsia it has been claimed that there is no histidinuria. There is less conspicuous histidinuria in many diseases involving the pituitary gland, such as basophilism, acromegaly, and adiposogenital dystrophy.

Cystinuria. Small amounts of the amino acid cystine are normally excreted in the urine. In cystinuria there is excessive urinary excretion (Kennedy, Lewin, and Lunn). Under these conditions cystine, homocystine, and glutathione are completely oxidized but cysteine, homocysteine, and methionine are largely excreted as cystine (Brand, Block, and Cahill). In adults the cystine may precipitate in the urinary tract to form concrements. Rarely in young infants with cystinuria the cystine is deposited in the tissues (Beumer and Wepler).

Alkaptonuria. In this familial physiologic disturbance large amounts of homogentisic acid are secreted in the urine. There are no distinctive anatomic changes, and the patient rarely seeks medical advice because of the alkaptonuria. Feeding of tyrosine or phenylalanine increases the excretion of homogentisic acid, and 60 to 70 per cent of the theoretical recovery is secured. The urine turns black on exposure to air or on alkalization. In rats and guinea pigs excessive dietary phenylalanine causes alkaptonuria (Papageorge and Lewis), preventable in guinea pigs by an abundant intake of vitamin C (Sealock and Silberstein).

Ochronosis. In ochronosis there is a blue to brown pigmentation of the cartilages and other tissues of the body by a melanotic pigment (Scott and Moore). The condition is observed in patients with an alkaptonuria and in those who have used large quantities of phenol in the treatment of chronic ulcers. It is apparently associated with a disturbance in the metabolism of aromatic compounds (Oppenheimer and Kline).

Disturbances in the Metabolism of Nucleic Acid, Purines, and Pyrimidines

The nucleoproteins are conjugated proteins composed of basic proteins combined with nucleic acid. On hydrolysis a quantity of protein is split off as labile protein, while with further hydrolysis the remaining nuclein is split into a protein and nucleic acid. The nucleic acids are composed of phosphoric acid, a carbohydrate, and a nitrogenous group, either a purine or a pyrimidine. The characteristic nucleic acid of animals is thymonu-

be synthesized by the animal organism. The uric acid in the urine is derived from two sources—from nucleoprotein in the food (exogenous uric acid), and from breakdown in the cytoplasm of cells of the animal organism (endogenous uric acid).

Gout. Gout has been the subject of many dissertations and caricatures during the ages, but today the physician sees few cases of classical gout. However there are in the United States many persons with mild, unrecognized forms of gout.



Fig. 9. Gout. Tophi about the finger joints. (MacCallum: Textbook of Pathology.)

cleic acid, composed of phosphoric acid, *d*-2-ribodesose, two purines (adenine and guanine), and two pyrimidines (thymine and cytosine). Thymonucleic acid may be of two types, desoxyribonucleic acid and ribonucleic acid. The latter is found also in the cytoplasm and probably is concerned in the fabrication of protein.

Nucleic acid may be recognized in general by basophilic staining, and in particular by specific staining reactions such as the Feulgen stain before and after action by enzymes (Stowell).

The final product of the oxidation of the purines in man, anthropoid apes, birds, and reptiles is uric acid. In other species of vertebrates the product is allantoin. Purines may

Pathologic Anatomy. The characteristic pathologic changes of gout are in the cartilages of the body. Inspection of the knee or other joints reveals fine, white, irregular foci contained within the articular cartilage. The cartilage at these points is slightly thin and frayed. The white plaques result from the deposit of crystals of sodium urate. In more advanced stages the cartilage is completely eroded and the crystalline deposit is within the adjacent bone. Similar deposits are found in the periarticular tissues and in the synovia. There is a mild inflammatory reaction characterized by edema, cellular infiltration of lymphocytes and monocytes, and the formation of foreign body giant cells about the crystals. Similar deposits in the cartilage of

the lobes of the ear represent the classical tophi of gout (Brogsitter).

In many cases of terminal gout there is definite disease of the kidneys, either arteriolar nephrosclerosis or chronic glomerulonephritis. Occasionally the urates are deposited in the medulla of the kidney or form concretions within the pelvis or ureter.

Incidence. Gout is distinctly a disease of men, and the first changes usually appear during the fourth decade of life. A familial incidence is occasionally noted (Smyth and Freyberg).

Chemical Changes. During the acute phases of gouty arthritis and at times during the remissions there is an elevation of the blood uric acid to values from 6 to 12 mg. per 100 cc. of blood (normal is up to 3 mg.). The amount of uric acid in the urine may be normal or slightly elevated. There are no changes in the other products of nitrogenous metabolism.

Casual Factors. Many theories have been advanced in explanation of gout. The fact that the serum uric acid is increased in amount in a considerable percentage of the relatives of gouty patients indicates that there is a hereditary basis for the condition (Talbott). The theory that the deposits are nothing more than a reflection of the elevated uric acid in the blood is not tenable, because patients with uremia, eclampsia, and other lesions associated with hyperuricemia do not develop gout. In most patients with early gout there is no impairment of renal function, and hence it would appear that renal changes observed in terminal gout are an effect and not the cause of the metabolic dyscrasia (Coombs, Pecora, Thorogood, Consolazio, and Talbott). Detailed studies of the metabolism of uric acid in patients with gout indicate an increased formation of uric acid (Talbott and Coombs), borne out by the known association of gout with hemolytic jaundice (Deitrick). The reason for the association of gout with lead poisoning is not clear. There is little evidence that alcohol or type of diet has any influence on gout, although the ingestion of foods rich in purines may precipitate an attack of gout in the susceptible person.

Clinicopathologic Correlation. Gout is characteristically a disease with relapses and remissions. Following active use of the joints in walking or exercise a relapse may be precipitated. The joint is swollen, tender, and

extremely painful, presumably because of the deposit of urates within the cartilage and tissues. When the deposits are in the bone, they cause a resorption, and punched out areas may be seen on the x-ray plate. Gout is at times associated with polycythemia (Tinney, Polley, Hall, and Giffin).

Urate Deposits in the Kidney. In the kidneys of most newborn infants and rarely in adults the medullary rays are streaked with fine yellowish gray lines, incorrectly called "uric acid infarcts." Properly prepared sections show the deposition to be in the lumens of the collecting tubules without inflammatory reaction. Chemical analysis reveals both uric acid and urates. The cause is apparently an increased excretion of uric acid by the newborn (80 to 100 mg. daily) and by adults during diseases involving extensive destruction of nucleoprotein, such as pneumonia and leukemia (Wells and Corper).

Xanthine Calculi. A rare type of urinary calculus is one composed chiefly of xanthine. The pathogenesis is not clear (Kretschmer).

Disturbances in the Metabolism of Creatine and Creatinine

Creatine (methylguanidineacetic acid) is an essential chemical component of muscle—98 per cent of 120 gm. in the adult human body is in the muscles—and in the form of phosphocreatine is active in the chemical changes incident to contraction of the muscles. Creatinine, the anhydride of creatine, is a waste product and is excreted in the urine in amounts varying from 0.5 to 2 gm. per day, depending on the state of muscular development, the sex, the degree of activity, and the dietary intake of protein (Albanese and Wangerin).

Creatinuria. Creatine is constantly present in the urine of both male and female children and pregnant women (Smith), intermittently present in the urine of nonpregnant women, and characteristically absent from the urine of normal men. This difference in prepuberal and postpuberal life in men and women and in pregnancy is definitely related to the effect of the androgenic hormones. The intense creatinuria following ingestion of creatine by castrates can be suppressed by the injection of testosterone propionate (Coffman and Koch).

Creatine also appears in the urine in cer-

tain pathologic conditions: high protein diet, starvation, deficiency of dietary carbohydrate, diabetes, emaciation, diseases associated with fever, exophthalmic goiter, and the primary muscular dystrophies. In all of these there is a logical explanation related to an increased catabolism in muscle.

Aside from the degenerative changes in the skeletal muscles there are no other morphologic manifestations of creatinuria.

Disturbances in the Metabolism of Glucoproteins

In many animal tissues there is a clear, viscid, or slimy fluid, which on chemical hydrolysis yields a carbohydrate and a protein. These fluids are in general acidic, and hence stain with the basic dyes. Two types are recognized: that formed in tissues derived from mesoderm, known as "mucoid," and that elaborated by epithelial cells, designated as "mucin." This distinction is based not only on histologic appearance, but also on chemical composition. Mucoid yields on hydrolysis four components in equimolecular proportions: chondrosaminic, gluronic, acetic, and sulfuric acids; while mucin yields chitosaminic, glucuronic, and sulfuric acids. The mother substances are known as "chondroitin sulfuric acid" and "mucoidin sulfuric acid" respectively (Levene).

Disturbances in the Secretion of Mucin. In the respiratory and alimentary tracts and in some of the other hollow viscera normal function depends on secretion into the lumen of a mucin of proper fluidity.

Decreased Secretion of Mucin. In the early stages of most inflammations, throughout the course of a few specific inflammations, and following the administration of certain drugs such as atropine there is a decreased secretion of mucin on the epithelial surfaces. The person is aware of dryness of the nose and mouth, as in the earliest hours of an attack of the common cold. General dehydration brings about a similar decrease in secretion from the mucous membranes.

Increased Secretion of Mucin. In most inflammations of the mucous membranes there is an increased secretion of mucin—catarrhal inflammation. Notable examples are the abundant clear viscid secretions from the nose on the second and third days of a common cold, and the admixture of thick mucus with

the intestinal content in dysentery. Microscopic examination reveals distention of the epithelial cells with globules of a palely basophilic, stringy material (mucin coagulated by the fixatives), filling of the lumens of the glands and hollow viscera with a similar material, variable cellular infiltration of adjacent tissue, dilatation of the smaller blood vessels, and separation of the elements of the tissue by exuded fluid.

In a rare malignant tumor of epithelium, the neoplastic cells retain the capacity to form large amounts of mucin. These tumors are designated as "mucinous carcinomas" (not colloid or gelatinous carcinoma). The individual tumor cells may each be distended with a globule of mucus, or the entire acinus may be distended or disrupted by extracellular mucus.

Alterations in the Fluidity of Mucin. In a few instances not only is there hypersecretion of mucin, but the secretion is unusually thick and viscid. Notable examples of this are tracheobronchitis in infancy and asthma. The bronchi are filled with almost solid casts of mucus, and in microscopic sections the compact basophilic acellular material is easily demonstrable. In young infants inspissation of the secretions in the salivary and pancreatic ducts and in the respiratory and alimentary tracts has been ascribed to a basic defect in the parasympathetic nervous system resulting in the formation of thick secretions (see section on cystic fibrosis of the pancreas, p. 669).

Disturbances in the Elaboration of Mucoid. From most tissues derived from mesoderm small or large quantities of chondroitin sulfuric acid can be isolated chemically, but it is not demonstrable as a histologic entity except in the mucoid tissue of the umbilical cord. Under pathologic conditions, especially in certain tumors such as fibromas and mixed tumors of the salivary glands, the stroma becomes relatively acellular, and the intercellular substance becomes bluish gray and translucent, and appears microscopically as a basophilic stringy material. In some instances this probably represents a true prosoplasia of the neoplastic cell to a myxoblast with the formation of mucoid, while in others it is more likely a degeneration of collagen so that it takes on the gross and microscopic appearances of mucoid.

Disturbances in the Metabolism of the Chromoproteins—Melanin

Chromoproteins are highly colored, conjugated proteins, the most important of which is melanin, the normal pigment of the skin, hair, and eyes of animals. The entire skin of a Negro contains about 1 gm. of melanin.

Demonstration in Tissue. Melanin confers a red, brown, or black coloration on tissues, depending on the amount and distribution, and possibly on the exact chemical nature. In sections it appears as fine, light brown granules or globules, intracellular or extracel-

Metabolism. Under normal conditions melanin is excreted in the urine and possibly in the intestine, but not in sufficient quantities to identify. If excessive amounts are formed, the urine is dark, or turns black on exposure to air or on the addition of oxidizing agents. The colorless precursor is known as "melanogen." In persons excreting melanin or melanogen, pigment granules may be found in the epithelium and in the lumen of Henle's loop and of the collecting tubules. Occasionally casts in the urinary sediment contain pigment. Similar pigment is also present in the

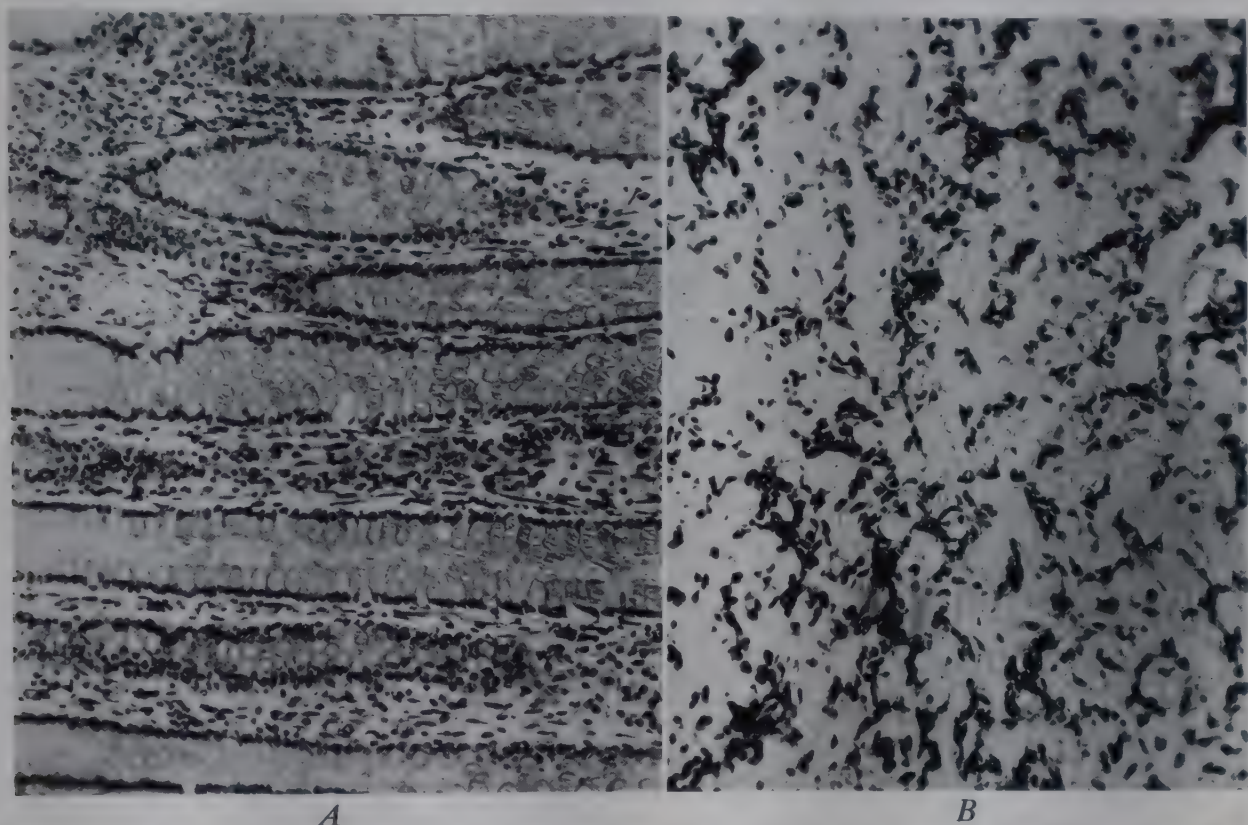


Fig. 10. *A*, Excessive formation of mucin in the epithelial cells of the colon. *B*, Mucoïd in a mixed tumor of the parotid gland.

lular. The granules do not stain with reagents used to demonstrate iron, but are argyrophilic. Chemical extraction is difficult except with strong acids or alkalis that probably alter the structure.

Formation. Melanin may be found in cells capable of forming it (melanoblasts), or in wandering or fixed cells that have phagocytized it (melanophores). All melanoblasts in the human body are derived from the neuroectoderm. Identification is easily accomplished by means of the histochemical technique known as the "dopa reaction," discovered by the renowned Swiss dermatologist, Bloch. If properly prepared sections of skin are placed in 1 per cent DihydroOxyPhenylAlanine, numerous pigment granules appear in cells of the basal layer, because of the presence in these cells of an oxidase.

phagocytes of the liver, spleen, and lymph nodes (Jacobsen and Klinck).

Melanin in Pathologic Conditions. *Hyperpigmentation of the Skin.* The pigmentation of the skin, diffusely or as freckles, following exposure to solar radiation or ultraviolet radiation is the simplest example of an increased formation of melanin. In Addison's disease, resulting from destruction of the adrenal cortex, there is hyperpigmentation of the skin, especially in the folds of the axilla, groin, back of the neck, and beneath the breasts.

Albinism. This is an inherited mendelian recessive condition characterized by complete or partial absence of the usual body pigments (Wakefield and Dellinger). Dopa stains of the skin show no melanoblasts. There are no other pathologic changes. Partial albinism—the piebald Negro or the "leopard man" of the

sideshows—is at least in some instances genetically dominant (Keller). Albinism in animals is well illustrated in white mice, rats, and rabbits, and in the seasonal whiteness of some arctic animals. Acquired local depigmentation, or vitiligo, is associated with many diseases,

nevi and malignant melanomas—the neoplastic cells are dopa-positive and frequently retain the ability to synthesize melanin. These tumors are brown or black.

Pigmentation of the Adrenal Cortex. Pigmentation of the zona reticularis of the



Fig. 11. Section of skin stained by the dopa reaction from a patient with dermatitis associated with ingestion of phenolphthalein. (Case reported by Weiss, R. S., and Kile, R. L.: Arch. Dermat. and Syph., Vol. 32.)

follows severe trauma to the skin, and occurs as a primary disease (Fig. 12).

Melanosis Coli. At times in chronically constipated persons and in patients with longstanding mechanical intestinal obstruction, the mucosa of the colon is black because of the deposition of light brown granules and globules in phagocytic cells in the interstitial tissues of the mucosa. The cells are dopa-negative, but the pigment is argyrophilic and non-iron-containing. The condition is probably a manifestation of altered excretion of normal melanin by the colon or absorption of melanin synthesized by bacterial or enzymatic action in the intestinal lumen. The frequent association with prolonged use of anthracene laxatives is probably not a cause-and-effect relation. It should be distinguished from pseudomelanosis coli, in which hydrogen sulfide formed in the lumen after death reacts with the iron of disintegrating hemoglobin to form black iron sulfide (Jacobsen and Klinck).

Melanoma. In tumors of the melanoblast—

adrenal in older people probably represents the formation of melanin by cells of the medulla and phagocytosis by the cortical cells.

Irreversible Changes in Intracellular Proteins

Necrosis is the pathologic death of a cell or a group of cells in contact with living cells. It differs from necrobiosis, the physiologic death of cells as in the constant replacement of the epidermis, and from somatic death which is death of the entire animal organism.

Criteria of Necrosis. Life is recognized in cells by certain phenomena generally attributed to living matter: respiration, locomotion, and reproduction. Conversely death is the absence of all these properties. Superficially the distinction appears definite, yet on more detailed study there are seen to be many transitional phases and paradoxes. Spermatozoa may be frozen at -70°C . for many months and in this state exhibit no demonstrable metabolism, yet they are fully alive and

capable of reproduction when warmed to body temperature.

General Mechanism of Production of the Changes of Necrosis. Most of the changes recognized both grossly and microscopically as those of necrosis are produced by the action of intracellular enzymes, particularly of the proteases. This may be shown if two pieces of tissue are taken from an animal, one placed in boiling water for a moment, and then both transplanted into the subcutaneous tissue. Within a few hours or days the un-boiled tissue undergoes necrosis, while the boiled tissue may retain the normal staining reactions and appearance for over a month except at the edge where the tissue fluids of the host containing enzymes come in contact with it. It follows that the anatomist and chemist must look for changes related to a breakdown or hydrolysis of the complex protein molecules as the criterion that death has occurred.

Microscopic Changes of Necrosis. *Changes in the Nucleus.* The initial step in the hydrolysis of nucleoprotein liberates nucleic acid and protein. It is generally assumed that nuclei stain with the basic dyes because the nucleic acid is not completely saturated with protein. It follows that if nucleic acid is freed from combination, the nucleus would stain more intensely. This is actually observed, and is designated as "pyknosis." The nucleus is somewhat smaller than normal and stains as a uniform, dense mass with a smooth or crumpled nuclear membrane. At the same time the nuclear membrane may undergo dissolution and the free nucleic acid be distributed throughout the cell in small masses—a condition known as "karyorrhexis" (Fig. 13, *A*). With further hydrolysis the nucleic acid is split into phosphoric acid, purine bases, and other substances. If the original assumption that nuclei stain because of nucleic acid is correct, this stage would be seen as a decrease in the intensity of the stain. Such an appearance is frequently seen in necrotic tissues, and the term "karyolysis" is applied (Fig. 13, *B*). Simultaneous histologic and chemical studies show that there is no stainable nuclear substance when 25 per cent of the nucleic acid has been hydrolyzed (Corper).

Changes in the Cytoplasm. The primary change in the cytoplasm is cloudy swelling. The cells are enlarged, and the cytoplasm is

finely granular. After some hours or days larger granules appear, or the cytoplasm is fused into a dense, homogeneous, acidophilic globule. At the same time or a little later the cell membrane is lost and the cytoplasm fuses with that of contiguous cells or appears as a formless mass. Gradually the necrotic material undergoes complete autolysis and passes into solution, or is phagocytized by mononuclear cells.



Fig. 12. Patient with vitiligo. (Photograph by courtesy of the Barnard Free Skin and Cancer Hospital.)

Physicochemical Changes in Necrosis. As soon as death occurs; the selective permeability of the cell wall is lost and all substances diffuse freely in both directions. This change in permeability in plant cells alters the turgor of the cells so that the plant wilts. Dyes of large molecular size such as trypan blue do not pass into normal cells, and hence may be used to detect dying or necrotic cells in experimental animals. Similarly there is a decrease of electrical resistance, and as the complex molecules are broken into multiple smaller molecules, the osmotic pressure and the electrical conductivity are increased.

Causes and Types of Necrosis. From what

has been said in the preceding paragraphs, it is evident that the agents which cause necrosis are those which limit the supply of oxygen and food or the removal of waste products, which physically destroy cells, or which block

supply to a part depends on the location of the tissue and the mechanism of the block of the circulation. Three types of ischemic necrosis are recognized: infarct, decubitus, and gangrene.

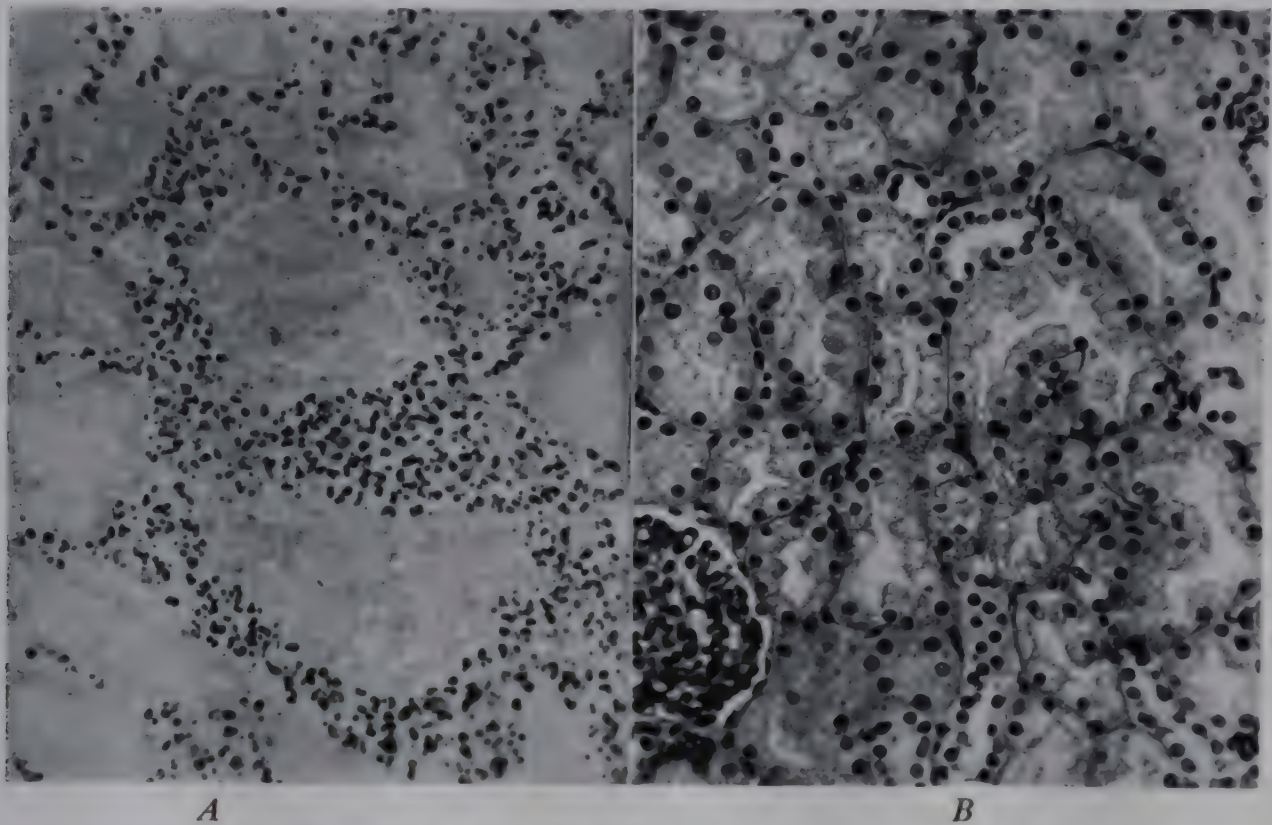


Fig. 13. *A*, Karyorrhexis in the edge of an infarct of the kidney. *B*, Karyolysis in cloudy swelling of the renal epithelium. There is variation in the chromatism of the nuclei.

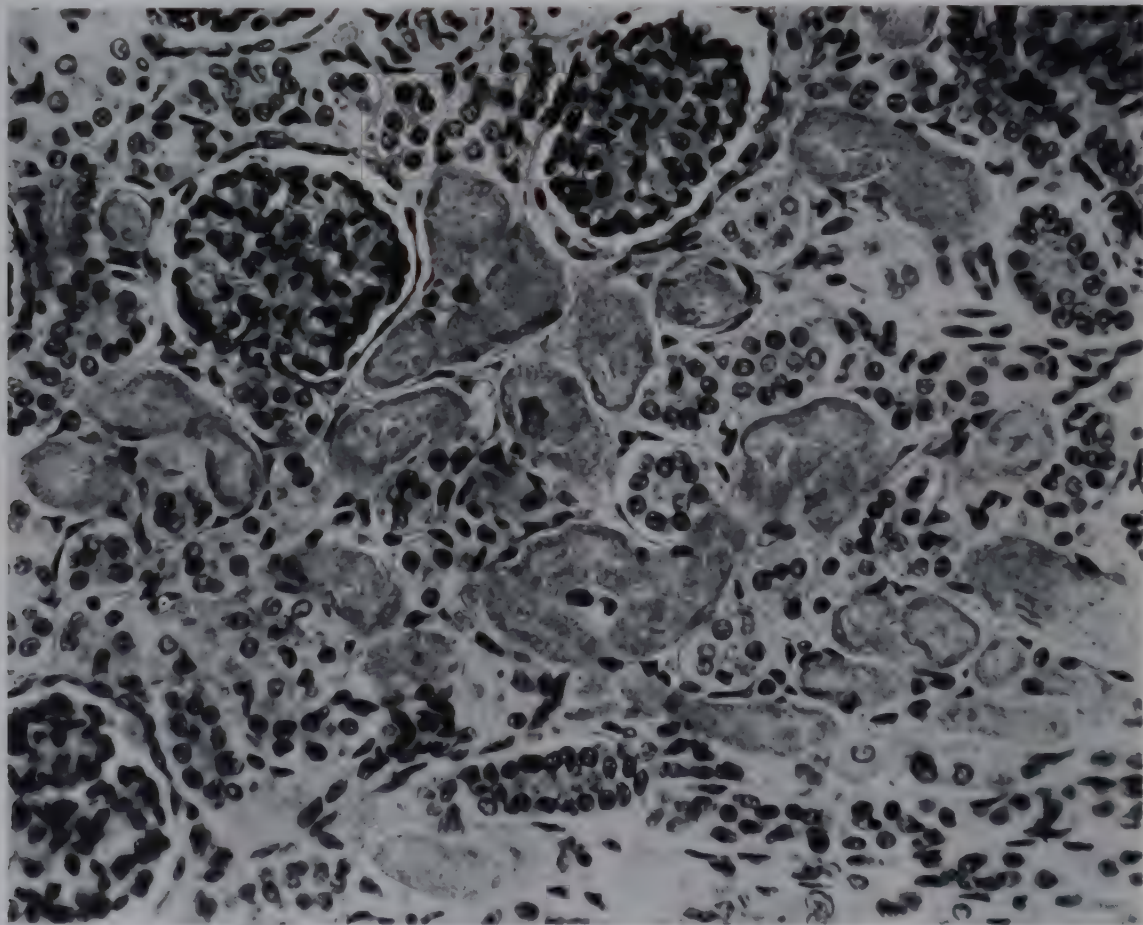


Fig. 14. Necrosis of the renal epithelium in mercuric chloride poisoning.

or poison enzymatic processes necessary for life. In practice these agents may be arranged in four categories: ischemia, physical agents, chemical agents, and micro-organisms.

Ischemia. The result of a cessation of blood

INFARCT. If a part completely surrounded by living tissue undergoes ischemic necrosis, it is known as an "infarct." Because the tissue supplied by any one vessel is conical, the infarct is roughly conical, with the apex at the

occluded vessel. At first the tissue is swollen, soft, grayish yellow or red, and moist. Within a few hours or days it becomes distinctly yellow, firm, and dry, and occupies a space greater than the original living tissue. Hence it bulges from the natural surface and from the cut surface. Microscopically, the outlines of the former structures are easily seen, and with special stains fibrin or fibrinoid is demonstrable in the interstitium. Because of these characteristics it is known as "coagulation necrosis." In a few organs, notably the brain, the infarct undergoes rapid liquefaction, and the term "liquefaction necrosis" or "colliquation necrosis" is applied (see Chap-

from that which results from the activity of bacteria—"wet gangrene."

Physical Agents. Physical agents which cause necrosis are penetrating or nonpenetrating wounds and radiant energy. Radiant energy includes electricity, infra-red rays, ultraviolet rays, and roentgen rays, and the rays of radium (see the section on diseases caused by physical agents, p. 474).

Chemical Agents. The chemical substances causing necrosis are exogenous or endogenous. Exogenous chemical agents may act locally or be carried by the blood to some internal tissue; for example, following ingestion of mercuric chloride there is necrosis of



Fig. 15. Infarct of spleen. (MacCallum: Textbook of Pathology.)

ter VIII on disturbances in the fluidity of the blood).

DECUBITUS. After a person lies in one position for a long time the skin and subcutaneous tissues over the prominences are compressed, and the circulation in the part is impaired. Necrosis results. The continuity of the skin is interrupted and an ulcer is formed which is known as a "decubitus" or a "decubital ulcer." These ulcers are most common over the sacrum, buttocks, and heel, and in debilitated and emaciated persons. Secondary infection is frequent, and a fatal pyemia or septicemia may ensue. The stercoral ulcer in the rectum, formed by pressure from a firm fecal mass, is an analogous lesion.

DRY GANGRENE. In an extremity connected only on one surface with living tissue, occlusion of an artery results in gangrene. The tissue gradually loses fluid and becomes mummified. The line of demarcation is generally sharp, and the contiguous living tissue is swollen and hyperemic. The adjective "dry" is used to distinguish this type of gangrene

the mucosa of the stomach caused by the direct coagulative action of the mercuric salt in the gastric contents. After absorption the mercury is selectively excreted by the kidneys and colon. The higher concentration in the organs induces necrosis of the renal epithelium and of the colonic mucosa. Other substances have no effect locally but produce severe changes in some distant tissue. Thus inhaled chloroform has no deleterious effect on the lungs, but causes necrosis of the cells of the central part of the lobules of the liver. In contrast, phosphorus affects the peripheral part of the hepatic lobule. Endogenous chemical agents are present in the toxemias of pregnancy, the hepatorenal syndrome, and other conditions. By evaluation of the location and character of the necrosis it is possible frequently to determine the cause.

Action of Micro-organisms. Many bacteria elaborate exotoxins or endotoxins that cause necrosis. As the tubercle bacillus proliferates locally the tissue is converted into a circumscribed, yellow, dry, friable mass, known as

“caseous necrosis.” Similarly the treponema of syphilis locally may produce a focus of grayish yellow, dry, rubbery tissue, designated as “gummatous necrosis.” The bacteria of gas gangrene secrete toxic substances that kill adjacent cells, and at the same time the bacteria form gas in the tissues.

The mechanism of action of the pyogenic cocci and the formation of pus is probably a mixed reaction. Toxins of the bacteria kill some fixed tissue cells, and in addition many leukocytes attracted to the region are killed and liberate excessive amounts of proteolytic ferments. These ferments in turn digest the tissue and thus form the characteristic thick yellow pus—a type of colliquation or liquefaction necrosis.

SOMATIC DEATH

From a clinical standpoint somatic death means cessation of respiration and cessation of cardiac action. For a variable period of time after somatic death the tissues are alive and capable of physiologic response to adequate stimulation. Gradually a series of irreversible changes ensues. The more important of these are algor mortis, rigor mortis, livor mortis, clotting of the blood, autolysis, and putrefaction. In medicolegal investigations a correct evaluation of these changes is the basis for the estimation of the time of death.

Algor Mortis. With the cessation of metabolism the source of heat to maintain the temperature of the body above that of the environment is lost. Consequently there is a gradual decrease in temperature. The velocity of the decrease depends on the size of the body, the amount of subcutaneous fat, the covering of the body with clothing, the humidity and wetness of the surroundings, the rapidity of circulation of air, and other factors. In general there is a loss of 3.5° F. per hour for three hours, 3° F. per hour for the next six hours, and 1.2° F. per hour indefinitely thereafter until the environmental temperature is reached (Moritz and Lund).

Rigor Mortis. Within two or three hours after death the muscles become stiff. The process begins in the muscles of the head and neck and spreads to those of the trunk and extremities. The maximum stiffness is reached in four to twelve hours, and in ten to forty-eight hours the muscles are again flaccid. A high fever, violent physical exercise, or ex-

haustion just before death, and a high environmental temperature accelerate the process, while it is delayed in persons with wasting diseases and in bodies exposed to low environmental temperature. The cause is probably the accumulation of acids and swelling and precipitation of certain proteins in the muscles at a pH of 6.3 to 6.6. With further increase of acidity the proteins return to solution and rigor is lost.

Livor Mortis. As the force driving the blood through the vessels ceases, the liquid blood gradually settles into the dependent parts of the body. In persons with cardiac failure, livor may be evident before death, but in most persons the characteristic red mottling becomes definite one to two hours after death. After ten to twelve hours, later if the temperature is low, the livor becomes fixed and does not disappear on pressure or change when the body is moved.

Clotting of the Blood. The stagnant blood gradually clots into a red, elastic “cruor” mass, filling the vessels and all of the branches. In the heart the clot is entangled in the valves and muscles. The postmortem clot is to be distinguished from an antemortem clot or thrombus by the red color, the elasticity, and the nonadherence to the wall. In persons with gradual failure of the circulation, clotting may begin before somatic death, and the characteristic layered agonal clot is formed. There is a dependent red layer of red cells and fibrin, and a superior yellow translucent layer of white cells and fibrin.

Autolysis. The intracellular enzymes of tissues inadequately supplied with blood are activated. Hence after death there is gradual digestion of the complex protoplasmic constituents—a process known as “autolysis.” Bacteria play no part in it. The velocity of autolysis varies with the tissue. In the intestine there is beginning digestion of the mucosa within a few minutes after death. The superficial epithelium is lost. There is loss of nuclear staining, and the cellular outlines are indistinct. Changes in the pancreas appear early, and tend to be more evident in some foci than in others. In the prostate there is desquamation of the epithelium. In the kidney the epithelium of all tubules is in part desquamated. The nuclei stain poorly, and the cells are indistinct. The interstitial tissue is prominent, and the elements are separated.

Autolysis is to be distinguished from ante-mortem degeneration and inflammation by the complete absence of reaction.

Within the blood vessels the red cells are broken down, and the liberated hemoglobin stains the intima of vessels, the cardiac valves, and the serous membranes—a lesion known as “postmortem imbibition.”

Putrefaction. Putrefaction is the change in the dead body caused by invasion of saprophytic bacteria, notably those in the intestinal canal. The volatile products formed by the action of the bacteria are responsible for the offensive odor of putrefied bodies. The discoloration, most notable in the abdominal wall, is due to iron sulfide and methemoglobin formed by the interaction of hemoglobin and the products of the bacteria. As putrefaction and autolysis progress over a period of months and years, definite species of insects are attracted to the body. In some instances by identification of the species present, it is possible to estimate the time interval between death and the finding of the body, up to about four years.

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III

Disturbances in the Action of Enzymes

During the past thirty years as biochemistry has become increasingly a dynamic science, many new methods for the study of enzymes have been developed. There are essentially three procedures for the study of enzymes in tissue: static chemical, dynamic chemical, and microtechnical.

Static Chemical Demonstration. In this method, an aliquot sample of tissue is removed from the living or recently dead animal organism and the absolute or relative amount of enzyme determined by the action on a known amount of substrate.

Dynamic Chemical Demonstration. This is essentially the measurement of activity of a surviving tissue slice in a Warburg or similar apparatus under known conditions.

Microtechnical Demonstration. In contrast with the other two methods, which localize enzymatic activity to a tissue, this procedure identifies the cell in which the activity is present. Tissue is fixed in solutions which do not destroy the enzyme. Sections are exposed to the substrate in the presence of a soluble substance which will form a precipitate with the end product of enzymatic action. Finally, the insoluble compound is converted to a colored substance which can be recognized.

Although many important facts which have been discovered by the two chemical methods could be presented here, it is desirable to limit the discussion to the microtechnical demonstration, which might be described under the title of "Cytochemical Enzymology."

Alkaline Phosphatase

Technique. Tissue is fixed in 95 per cent alcohol and paraffin sections prepared. Deparaffinized sections are incubated at 37° C. in a solution containing a soluble phosphate—sodium glycerol phosphate—and a soluble

calcium salt (calcium nitrate) at pH 9.0. Finally the calcium phosphate is converted to a silver salt (Gomori).

Normal Distribution. Alkaline phosphatase is most abundant in the epithelium of the small intestine, in the epithelium of the proximal convoluted tubules of the kidney, in osteoblasts, and in endothelium (Kabat and Furth).

Changes in Disease. Choline deficiency in young rats leads to a decrease in the demonstrable alkaline phosphatase in the renal epithelium (Wachstein). In nephrosis induced by chemicals such as mercuric chloride and uranium nitrate, there is no reduction in the renal epithelium even when necrotic, but the regenerated cells contain little alkaline phosphatase (Breedis, Flory, and Furth). The epithelium of the kidney in chronic nephritis is almost devoid of alkaline phosphatase (Gomori). Within two to five days after ligation of the ureter, alkaline phosphatase disappears from the renal epithelium (Wilmer).

Acid Phosphatase

Technique. The method of demonstration of acid phosphatase is essentially that of the alkaline type, except that fixation is in cold acetone, the lead salt is used, and the reaction is carried out at pH 5.0.

Normal Distribution. The presence and amount of acid phosphates vary between individuals and between species. In general it is most abundant in prostatic epithelium and in the reticulo-endothelial elements of the spleen, with lesser amounts in hepatic cells, gastric and intestinal epithelium, and adrenal cortex and medulla.

Changes in Disease. In acute inflammations there is a depletion of acid phosphatase, while in chronic inflammations the macrophages are

often rich in enzyme. The epithelium of nodular hyperplasia of the prostate gives a strong reaction (Gomori). Starvation causes an increase of acid phosphatase in the bile capillaries (Deane). The cells of prostatic carcinoma, both in the primary site and in the metastases, contain abundant acid phosphatase (Woodward and Dean).

renal epithelium, secretory cells of pancreatic acini, intestinal epithelium, adrenal cortex, and adipose tissue.

Changes in Disease. Inflammation does not greatly alter the lipase content of cells unless there is necrosis, in which case the enzyme disappears. The hepatic cells in cirrhosis contain an increased amount. Cells with fatty

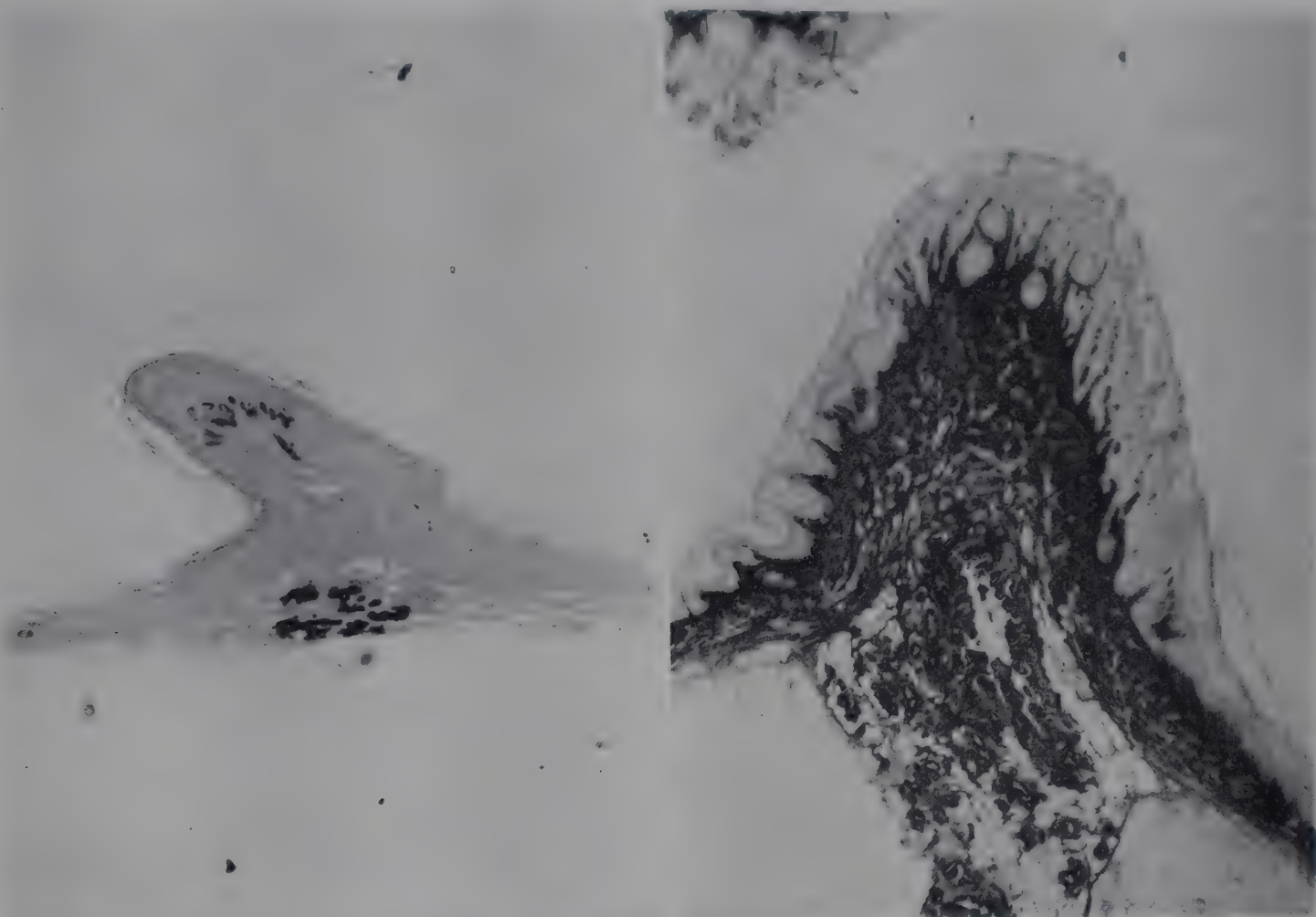


Fig. 16. Breast of adult guinea pig under normal conditions (left) and after stimulation with an estrogenic substance (right). The two photographs are at the same magnification. Note the great increase in glandular epithelium and in the alkaline phosphatase in the glandular epithelium which is stained black. (Photographs by courtesy of Dr. A. I. Lansing, identical with photographs in *Anat. Record*, August 1950.)

Other Phosphatases

Recent investigations suggest that there are not two clearly defined phosphatases—acid and alkaline—but rather a wide variety acting on different substrates at different pH's. Further investigation is needed (Deane).

Lipase

Technique. Tissue is fixed in cold acetone and paraffin sections prepared. The substrate is an aqueous solution of the esters of palmitic and stearic acid, and the hydrolyzed acid is captured with calcium chloride, which is converted to lead sulfide (Gomori).

Normal Distribution. Lipase is most abundant in hepatic cells, broncheal epithelium,

degeneration in kidney, heart, and liver are free of lipase or have only a small amount. Most tumor cells are devoid of lipase activity. In nephrosis, changes in lipase are similar to those of alkaline phosphatase (Wachstein).

Miscellaneous Enzymes

Many other enzymes have been described but microtechnical methods for their demonstration in animal tissues have not been fully developed. Recently Stowell has stained sections with pyronine-methyl green before and after action by ribonuclease to determine the amount of ribonucleic acid in cells.

The use of the enzyme which polymerizes substrates to melanin for identification of melanoblasts has been described (p. 21). The

identification of peroxidase granules in cells of the myeloid series is a valuable procedure (Goodpasture).

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IV

Disturbances in the Metabolism of Carbohydrates

For normal metabolism, carbohydrates should constitute about 60 per cent of the caloric intake. If the proportion falls below 10 to 20 per cent, ketosis develops.

Requirement and Source of Dietary Carbohydrate. Most dietary carbohydrate is in the form of the complex polysaccharides, i.e., starch. In each twenty-four hours an average man requires about 250 gm. of carbohydrate in the form of glucose. This must be derived either from the diet or from the stores, which normally consist of about 100 gm. in the liver, 250 gm. in the muscles, and 20 gm. in the extracellular fluids (Soskin).

Digestion and Absorption of Carbohydrate. Polysaccharides in the food are hydrolyzed by enzymes in the salivary and pancreatic juices to monosaccharides. These are absorbed at a constant rate, regardless of the total amount in the intestine. Each monosaccharide passes into the blood at a different rate. If the velocity of absorption of glucose is arbitrarily set at 100, the velocity of absorption of galactose is 10 per cent of this figure; of levulose 43 per cent, of mannose 19 per cent, of xylose 15 per cent, and of arabinose 9 per cent (Cori).

Storage and Conversion of Carbohydrate. Carbohydrate is stored principally in the liver and the skeletal muscle. Formation of glycogen from glucose and levulose proceeds at an equal rate, and reaches a maximum two to four hours after ingestion. The conversion of galactose to glycogen is only one-third as rapid. These conversions probably occur in the liver. Advantage is taken of them as a test of liver function—the galactose tolerance test.

Interconversion of Other Foods to Carbohydrate. Certain amino acids, glycerol, lactic acid, and pyruvic acid are readily converted to carbohydrate by the liver and stored as glycogen.

Oxidation of Carbohydrate. The steps in the conversion of glucose to glycogen are phosphorylation in the sixth position to form glucose-6-phosphate, conversion of this to glucose-1-phosphate, and then polymerization to glycogen. Adenosine triphosphate is the carrier for phosphorus in these reactions. In the reverse order glycogen is broken down to glucose-1-phosphate, to glucose-6-phosphate, to phosphopyruvate, to pyruvate, and finally to either lactic acid or to carbon dioxide and water, depending on the presence of oxygen (Cori).

Demonstration of Carbohydrate in Tissue

Histologic Methods. Of the two carbohydrates in normal tissue, glycogen and glucose, only the former is histologically identifiable. Glucose is soluble in all reagents used for the fixation of tissue, and no stain has been developed for it. On the other hand, glycogen is insoluble in alcohol, and may be demonstrated in tissue by the Best carmine stain or some modification of it. The tissue is fixed in 95 per cent or absolute alcohol, cut in celloidin or paraffin, and stained with a specially prepared solution of carmine. After death, glycogen undergoes rapid hydrolysis to glucose, and it is necessary to fix the tissues as soon as possible. Under certain conditions the presence of glycogen may be presumed in sections fixed and stained by the usual techniques. All other factors being equal, large amounts of glycogen confer on the cytoplasm of the hepatic cell a reticulated or finely vacuolated appearance. Similarly, vacuolation of the nuclei is indicative of the presence of glycogen in the nuclei of the hepatic or other cells (Fig. 19A). So far as can be determined, this finding has no significance (Chipps and Duff).

Chemical Methods. The only satisfactory quantitation of the amount of glycogen in tissue is by chemical analysis (Graffin, Marble, and Smith).

from an infectious disease, has a greater chance of recovery if adequate amounts of glucose are given him. In many toxemias there is impaired glycogenesis in the liver (Holmes).

Effects of a Deficiency of Dietary Carbohydrate

As determined by rate of growth, weight of organs, histologic structure of the tissues,

Effects of an Excess of Carbohydrate

Excess of the Usual Dietary Carbohydrates.

In man long-continued ingestion of a diet rich in carbohydrate may lead to the clinical con-

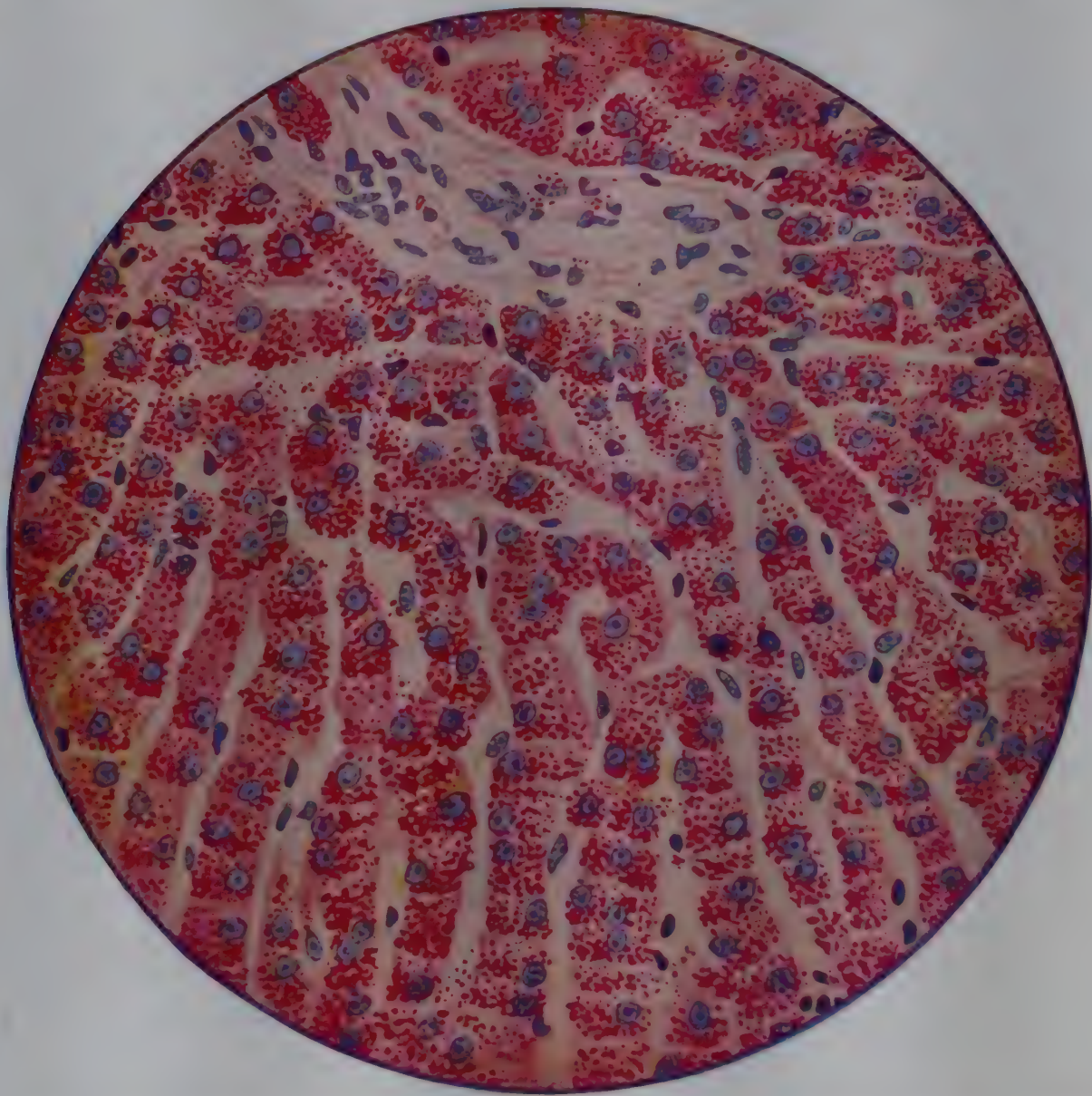


Fig. 17. Liver of a normal well-fed dog showing glycogen in cells. Best's carmine stain. (MacCallum: Text-book of Pathology.)

fertility, maintenance of carbohydrate stores, and respiratory quotient, there are no untoward effects of the consumption of a diet completely deficient in carbohydrate (Follis and Straight). This is not surprising in view of the known interconversion of the food-stuffs.

Relation to Resistance to Hepatotoxic Agents. If for any reason the carbohydrate stores of the liver are depleted, the animal organism becomes more susceptible to all sorts of hepatotoxic agents; thus a patient who is to receive an anesthetic, or who is suffering

from an infectious disease, has a greater chance of recovery if adequate amounts of glucose are given him. In many toxemias there is impaired glycogenesis in the liver (Holmes).

dition known as "intestinal carbohydrate dyspepsia." The anorexia, nausea, and abdominal distention are caused by gas in the colon. The stool is semi-formed, acid in reaction, and contains undigested starch. Pathologic studies of the condition have not been made.

In both man and animals the consumption of carbohydrate above the energy requirements results in the conversion of the excess carbohydrate to fat, deposit of this in the depots, and the development of obesity.

Excess of Lactose and Galactose. There is little valid evidence that reasonable amounts

of lactose are harmful to the growing infant, or that it or any other carbohydrate is the cause of diarrhea (Gerstley).

On the other hand there are rare instances of galactosuria associated with nutritional disturbances in which there is apparently an enzymatic defect in the conversion of galactose to glucose (Norman and Fashena).

Effect of Intravenous Sucrose. One form of therapy in traumatic injuries to the brain and in certain forms of renal disease with oliguria and edema has been the intravenous administration of solutions of sucrose or con-

in prevention has followed the use of diets low in carbohydrate.

Effects of a Decrease of the Blood Sugar

A value of 50 mg. or less per 100 cc. of blood for the postabsorptive blood sugar usually points to some organic lesion that has disturbed the metabolism of carbohydrate, and is designated as "spontaneous hypoglycemia" (Conn). The causes of spontaneous hypoglycemia are most varied: excess secretion of insulin by a tumor of the islands of

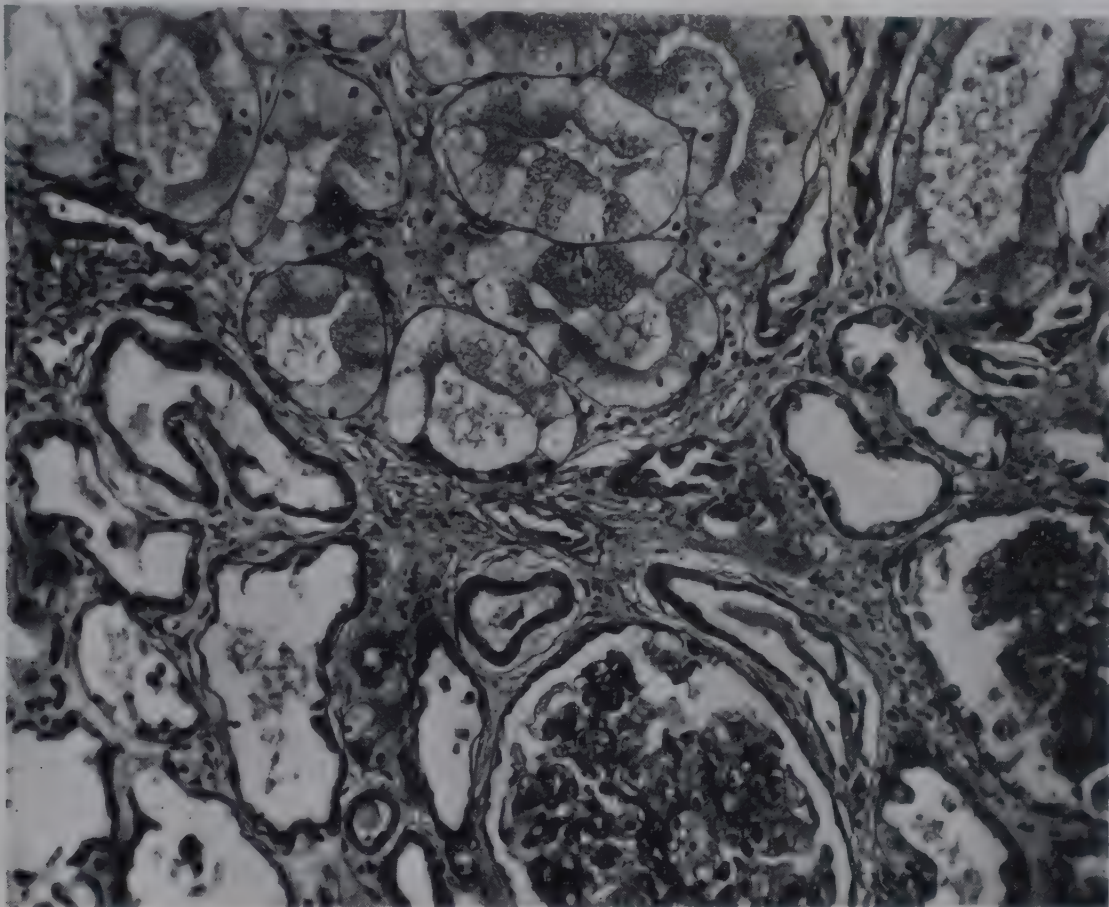


Fig. 18. Vacuolar degeneration of the renal epithelium following intravenous injection of sucrose.

centrated dextrose. In some of these patients, but not in all, there is a peculiar hydropic degeneration of the epithelium of the proximal convoluted tubules. The epithelium of these is greatly enlarged, and the lumen is decreased in size. The cells are filled with innumerable small vacuoles, and the cytoplasm is represented only by a delicate interlacing network (Fig. 18). The exact nature of this change has not been determined (Anderson; Rigdon and Cardwell).

Relation to Dental Caries. One of the theories of the pathogenesis of dental caries postulates the formation of acid in the mouth by lactobacilli acting on carbohydrates that have become adherent to the teeth. The acid in turn decalcifies the enamel. Considerable success

Langerhans, depletion of the stores of glycogen in the liver in diseases of that organ, inability of the body to mobilize stored glycogen as in glycogen disease, and hypofunction of the pituitary and adrenal glands as in Simmonds' disease and Addison's disease and in lesions of the hypothalamus. Fatigue and dizziness after exercise may be caused by hypoglycemia (Karlson and Cohn).

Pathologic changes have been observed in the brain in fatal cases of hypoglycemia. After a single injection of insulin and a precipitous fall in the blood sugar there are edema of the brain, congestion of the capillaries, isolated thrombi in the smaller vessels, and swelling of the ganglion cells. After repeated periods of or long-continued hypoglycemia, there are loss

of ganglion cells, diffuse or focal proliferation of astrocytes, focal or diffuse demyelination, accumulation of microglia, and perivascular hemorrhage. The lesions apparently result from cerebral anoxemia, and give rise to coma and convulsions (Lawrence, Meyer, and Nevin).

Disturbances in the Metabolism of Specific Carbohydrates

Complex polysaccharides in the diet are hydrolyzed in the intestine and converted to

glucose tolerance. There are no symptoms, but the history of diabetes in the families of patients with this condition is higher than in the general population. There is a lowering of the renal threshold for glucose. It accounts for about 10 per cent of all examples of mellituria (Blotner and Hyde).

Lactosuria in Pregnant and Lactating Women. During pregnancy the tolerance for lactose is increased, so that 20 gm. by mouth may not produce lactosuria. In the last trimester of pregnancy there is a minimal excretion of lactose, followed a few days after de-

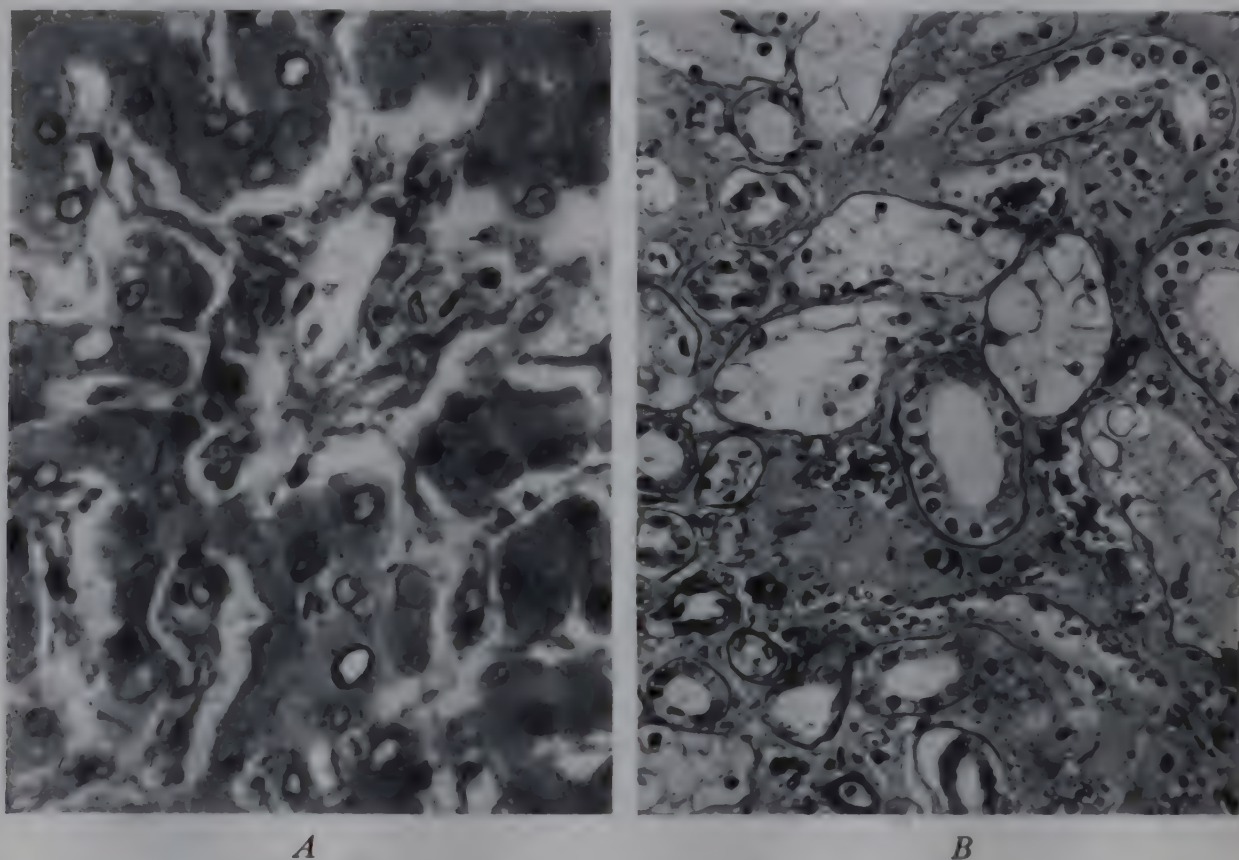


Fig. 19. *A*, Glycogen in nuclei of hepatic cells. *B*, Vacuoles of glycogen in the renal epithelium in diabetes mellitus.

glucose in the liver. Disturbances in metabolism may involve one or more of these processes.

Levulosuria. In this condition there is a failure of conversion of levulose to glucose, as well as an abnormally low renal threshold for levulose. So far as can be determined no deleterious effects follow (Marble and Smith).

Essential Pentosuria. Following the ingestion of large amounts of pentoses (fruits), a small amount of pentose may appear in the urine, but in chronic essential pentosuria there is a constant excretion of about 1 per cent. The condition is asymptomatic and probably harmless (Bowman and Beck).

Renal Glycosuria. In this condition there is glycosuria independent of diet, and a normal

livery by a greatly increased excretion, and finally gradual return to normal (Watkins).

Glycogen Disease

Normally the glycogen stored in the liver, muscle, and other organs is immediately available for maintenance of the blood sugar and for catabolism. In the condition known as "glycogen disease," or "von Gierke's disease," large amounts of glycogen are stored in the organs and, apparently, this glycogen cannot be mobilized. The liver is most frequently involved, and in most cases is the only organ showing gross change. Occasionally the heart is the only organ grossly involved, and this variety constitutes one of the types of idio-

pathic hypertrophy of the heart in children. Rarely the kidneys are affected, but almost always in association with similar changes in the liver.

Pathologic Anatomy. An organ that is the seat of glycogen storage is uniformly enlarged. The general shape of the normal organ is preserved. The capsule or the serous surface is smooth and not thickened; and there are no adhesions to the surrounding structures. The general architecture is preserved, and each element, such as the liver lobule, the cortex of the kidney, or the wall of the ventricle, is thickened or increased in size. The individual cells, myocardial fibers, hepatic cells, or renal

Chemical and Physiologic Aspects. During life there are certain distinct alterations in the metabolism of the person with glycogen disease. These are: a combination of hypoglycemia and ketosis in the fasting condition; an abnormal effect of epinephrine, expressing itself by absence of a distinct elevation of the blood sugar, a marked increase of the ketosis, and only a small elevation of the lactic acid content of the blood; an abnormal blood sugar curve after ingestion of glucose, unaccompanied by glycosuria; no diminution in tolerance to galactose and fructose; absence of so-called "initial insulin hyperglycemia"; normal values for the diastase activity of the blood and urine;

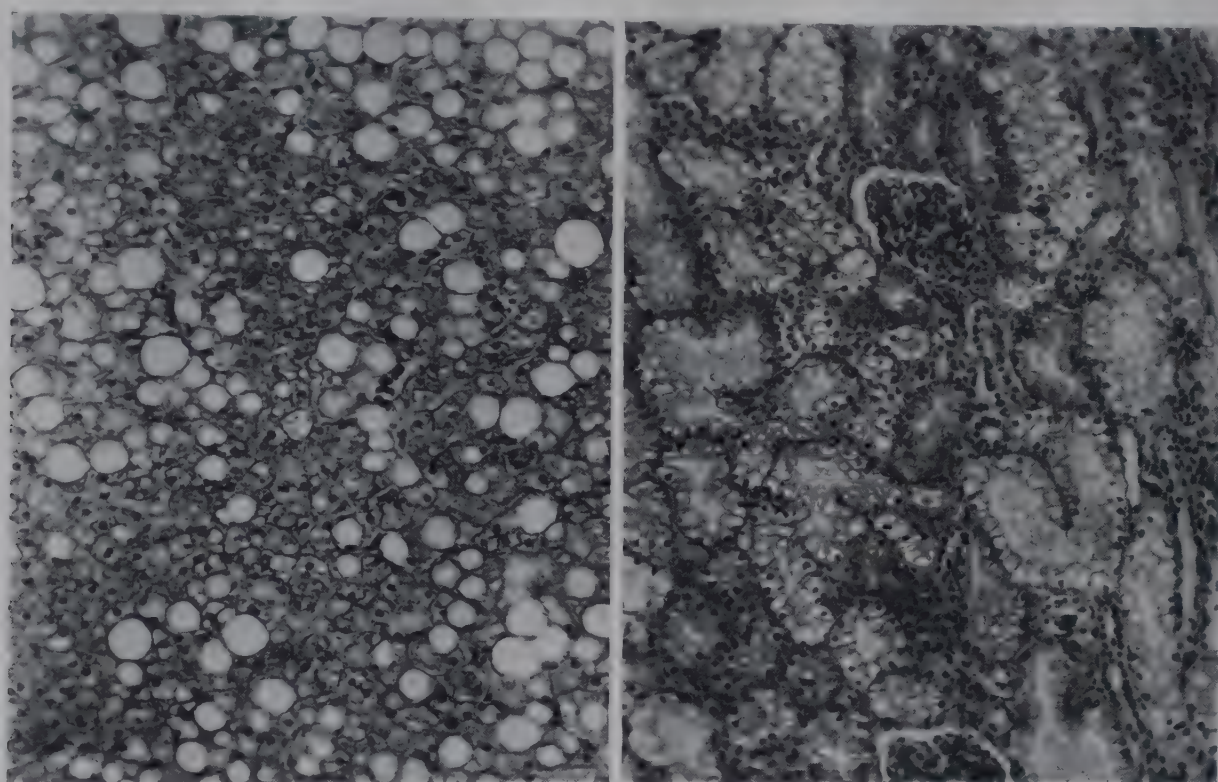


Fig. 20. Liver and kidney in glycogen disease. (Tissue by courtesy of Dr. Sidney Farber.)

tubular epithelium is increased in size as much as five times (Fig. 20). The cytoplasm contains innumerable small vacuoles, or it may have a reticulated appearance. In the heart the individual fibrillae within a fiber are arranged about the periphery of the cell. Occasionally there is a slight proliferation of connective tissue to constitute a cirrhosis or interstitial fibrosis. There is no cellular infiltration.

Changes in the other organs are inconstant. Hyperplasia of the adrenals and of the pituitary has been reported. The islands of Langerhans of the pancreas vary from a few small islands to unusually large ones. The skeletal muscle may show the same microscopic changes as the heart muscle.

normal diastase-activating effect of the serum; increased glycogen content of the blood not explainable by leukocytosis; normal glycogen-splitting activity of the blood serum; decreased glycogenolysis of the blood glycogen; normal plasma proteins; and hypercholesterinemia with normal relation between free and esterified cholesterol. Examination of the liver, either by biopsy or at autopsy, reveals a greatly increased amount of glycogen, which does not undergo glycogenolysis on standing, but can be hydrolyzed when normal liver is added to it.

Pathogenesis. From the anatomic, physiologic, and chemical facts listed, it would appear that the organs are capable of synthesizing a normal glycogen from simpler carbohy-

drates, but that they are unable to break down this glycogen for utilization.

Clinicopathologic Correlation. The enlargement of the liver and of the kidneys produces protrusion of the abdomen, and these organs are readily palpable. The enlargement of the heart and the consequent compression of the lungs may lead to respiratory embarrassment; and when the heart is involved, unexpected death, with dyspnea and cyanosis, is the rule. Adiposity may be explained as the result of conversion of carbohydrate to fat because of the overfilling of the depots of carbohydrates, or as the result of an infiltration of glycogen into the cells of the hypothalamus concerned with the metabolism of fat. Disturbances of growth may be an effect of the unavailability of carbohydrate or, less probably, a secondary effect of the hepatic changes.

Congenital Steatosis of the Liver. In an occasional patient with glycogen disease there is, in addition to the disturbance in the metabolism of carbohydrates, an excessive infiltration of fat in the hepatic cells. According to some, this condition may also occur independently of glycogen disease.

Glycogenic Tumors of the Heart. In infants glycogen may be deposited focally and give the appearance of a tumor (Batchelor and Maun).

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V

Disturbances in the Metabolism of Lipids

The term "lipids" is used to include the triglyceride esters of the fatty acids, cholesterol and cholesterol esters, and the phospholipids.

As a source of energy, fat and carbohydrate within wide limits can replace each other in isodynamic proportions, but an ideal diet for man contains between 20 and 30 per cent of the calories in the form of fat. Fats constitute the more expensive foods, and among the poorer classes, especially in Oriental races, and in war time when fats are needed for the manufacture of explosives, carbohydrates are substituted in order to maintain the caloric intake, and some of the effects of a high carbohydrate diet may be noted.

The Demonstration of Lipids in Tissue

Most lipids are soluble in the organic substances used for the preparation of paraffin and celloidin sections. Hence, the lipids in these microscopic preparations appear as a clear vacuole or space.

The usual technique for the demonstration of lipids is the preparation of frozen sections and staining with a fat soluble dye such as those of the Sudan series. Anisotropic or doubly refractile fat may be identified by examination of the frozen section in polarized light.

Less commonly, the fat is rendered insoluble by mordanting and then stained in celloidin sections. This technique is utilized in the study of the myelin sheaths of the nervous system.

Histochemical methods are available for the identification of certain fats. For example, soluble osmic acid is reduced by fat containing a double bond to insoluble black osmium which is seen in the section. Observation of crystalline fat under the microscope while

heating is an exact method for measurement of the melting point and hence identification.

Chemical methods depend on extraction of the tissue with solvents and fractionation into the various types of lipids.

Effects of a Deficiency of Dietary Fat —Starvation, Emaciation

Hunger and starvation have stalked the footsteps of man since the dawn of history. Modern agricultural methods and research have made a beginning in solving the problem, but much remains to be done. For example, it is estimated that in 1960, as compared to 1935–1939, the world will need an additional 63.5 million metric tons of cereals and 150 million metric tons of milk. At present there are about 1,940,000,000 acres of cropland used, and another 1,300,000,000 acres available if properly fertilized (Salter).

An animal organism deprived of an adequate intake of food derives energy first by the combustion of the carbohydrate stores, next by drawing on the fat stores, and finally by oxidation of tissue protein. In practice, the physician and pathologist rarely see the simple effects of a deficiency of dietary fat in man, but rather the effects of a deficiency of all dietary elements.

Pathologic Anatomy. The outstanding change in starvation or emaciation is loss of body weight up to 25 to 40 per cent of normal. The extremities are thin, and the skin is wrinkled and of poor turgor. Subcutaneous fat and other fat depots are minimal or absent, and in their place there is a peculiar yellowish brown, translucent tissue, designated as "serous atrophy of fat," especially prominent about the kidneys and in the pericardium. The fat cells are collapsed and separated from one

another by a protein-poor fluid (Fig. 21). The diminution in the size of the organs is not uniform. The greatest loss is in the subcutaneous fat (97 per cent), while the heart and brain decrease by only 3 per cent, and the skeletal muscle by 33 per cent. The liver and spleen lose 50 to 60 per cent, and the kidneys about 25 per cent. Microscopic study reveals a corresponding decrease in the size of the individual parenchymal cells and an increasing density of the cytoplasm. In children there is retardation of growth if the inanition extends over many months or years.

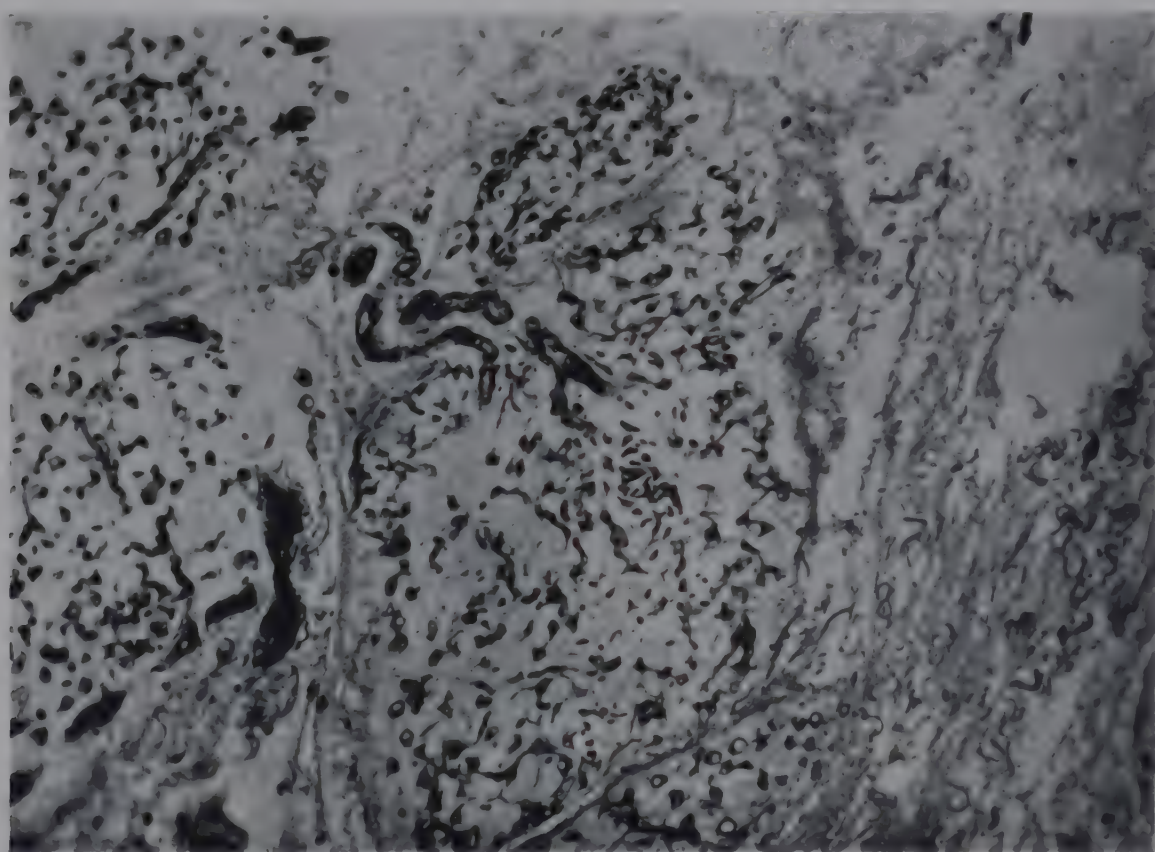


Fig. 21. Serous atrophy of a lobule of fat.

Physiologic and Chemical Changes. During the first few days of starvation, when stored carbohydrate is being utilized, there is a fall in the urinary excretion of nitrogen, followed on the third or fourth day by an increase, indicative of beginning oxidation of stored protein. After the fourth day there is again a decline to a constant level of about 6 gm. a day, until a premortal increase signals utilization of tissue protein. Urinary urea first rises and then progressively decreases. The burning of fats after the depletion of the carbohydrates leads to incomplete oxidation, appearance of acetone bodies and ammonia in the urine, and the chemical changes of acidosis. The abnormal metabolism in muscle results in a decrease of creatinine and an increase of creatine in the urine. This latter observation may serve as the

only objective evidence of starvation in the autopsy on a person found dead.

The Essential Unsaturated Fatty Acids. In rats a dietary deficiency of certain unsaturated fatty acids leads to changes in the skin and hair. There is some evidence that the serum fatty acids of patients with infantile eczema are less saturated than normal, and that ingestion of unsaturated fatty acids gives clinical improvement (Hansen, Knott, Wiese, Shaperman, and McQuarrie).

Fatty Liver in Emaciated States. Up to half of all patients in an emaciated state, depend-

ing on the cause, have a heavy deposit of fat in the liver. It is probable that this results from a metabolic defect caused by the inanition (Jones and Peck).

Effects of an Excess of Dietary Fat—Obesity

Obesity results from an increase of the subcutaneous fat, which frequently measures as much as 10 cm. or more in thickness. Similarly there are large deposits in the retroperitoneal tissues, in the fascial planes between the muscles, in the mediastinum, and about the kidneys. Certain organs such as the pancreas and heart may show the lesion designated as "fat infiltration." The normal lobules or muscle fibers are separated from one an-

other by fat cells. There is some evidence that the increase of body surface and body weight results in a slight increase in the size of the heart, and possibly of other organs whose sizes are determined by the rate of metabolism. The liver frequently increases in size, is yellow, greasy to the touch, and microscopically shows a large vacuole of fat in each liver cell.

Causes of Obesity. Most painstaking investigations have failed to disclose any abnormal process that accounts for the increased accumulation of fat in the obese person. The cause

cause of disease of the intestinal wall or mesenteric lymphatics. A distinction between the two types is easily made by analysis of the stool. In the former the fat of the stool is neutral fat, while in the latter free fatty acid is present. The specific diseases are discussed fully in Chapter LXXXII. There is, however, one apparently primary defect of absorption of fat, known as "intestinal lipodystrophy."

Intestinal Lipodystrophy. This condition is characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric

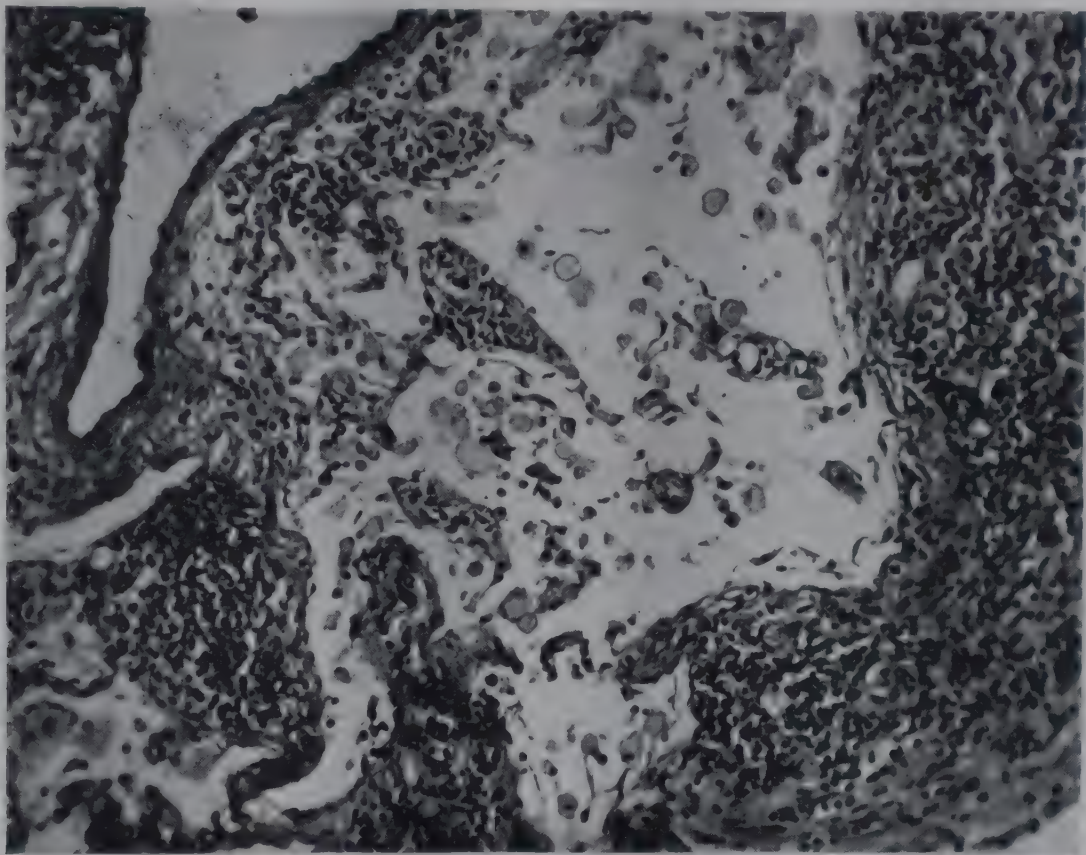


Fig. 22. Mesenteric lymph node in intestinal lipodystrophy. (Tissue by courtesy of Dr. Harry L. Reinhart.)

must therefore be a caloric intake greater than the need (Conn).

Effect of Obesity on Mortality. Obesity has a definite adverse effect on life expectancy and mortality, as shown in the following table for men between the ages of forty-five and fifty.

Pounds Overweight	Increase in Death Rate Over the Average in Per Cent
10	8
30	28
50	56
90	116

Disturbances in the Absorption of Fat

Failure of proper absorption of fat may be caused by an absence of the enzymes from the intestine because of disease of the pancreas or liver, or by defective absorption be-

lymphoid tissues. Small pedunculated cysts, filled with a thick, oily fluid, are scattered over the peritoneal surface. Some of the smaller cysts are firm and opaque, resembling the nodules of metastatic carcinoma on the peritoneal surface. The mesenteric lymph nodes are enlarged (Fig. 22), and the lymphoid sinuses are dilated and filled with an oily substance. The intestine is dilated, and the mucosa is thickened, firm, and red. Throughout the mucosa there are small elevated nodules, 1 to 2 mm. in diameter. Other organs show no characteristic pathologic change. The sinuses of the lymphoid tissue are dilated and filled with an amorphous, acidophilic debris, which, with specific stains for fat, shows the presence of free fatty acids and cholesterol. There is proliferation of fibrous tissue together with the deposit of large numbers of mononuclear

cells filled with droplets of fat. On chemical analysis the fat consists of approximately 60 per cent free fatty acid (Rosen and Rosen).

The lack of proper absorption of fat leads to steatorrhea and its secondary changes: distention of the abdomen, progressive emaciation, loss of strength, and microcytic anemia. The reason for the associated arthritis is not clear. Some of the symptoms may result from an inadequate absorption of the fat soluble vitamin A.

Disturbances in the Distribution of the Fat Depots

The smooth symmetry of the animal body is in large part dependent on the proper deposi-

tion of fat from the blood, the rate at which the organ can take up fat from the blood, the rate at which the organ can oxidize the fat, or after modification pass it on to other parts of the body, and the capacity of the organ to interconvert other foodstuffs to fat. In turn one or more of these factors are controlled by the dietary intake of fat and other foods, the activity of the endocrine glands, and the viability and catabolism of the individual parenchymal cells.

FATTY METAMORPHOSIS

Fatty Metamorphosis of the Liver. Fatty metamorphosis, a condition in which there is an increase of histologically demonstrable fat, influences the size, color, and consistency of an organ. The liver is typically slightly to

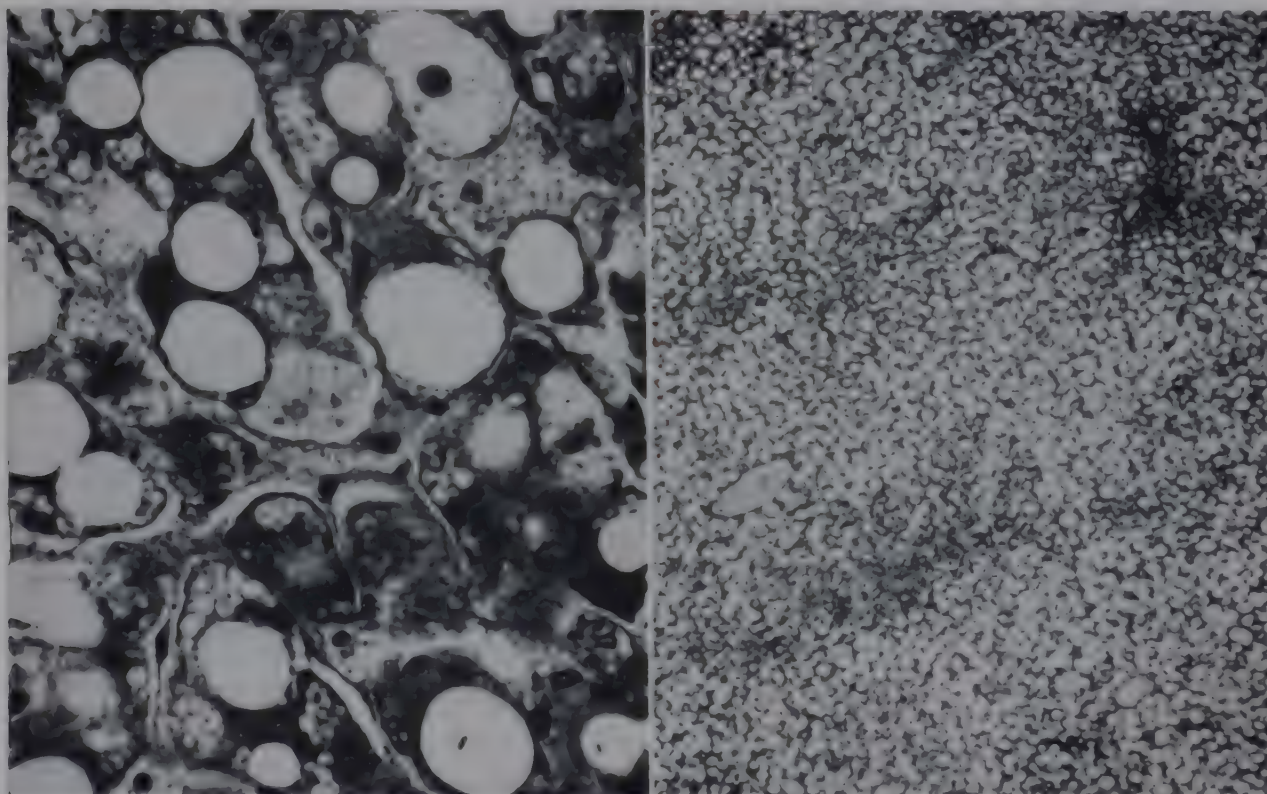


Fig. 23. Fatty metamorphosis of liver.

tion of the subcutaneous fat. In certain pathologic conditions the fat in the depots is deposited in only one part of the body, or irregularly. Most of these conditions are directly related to diseases of the endocrine glands, and will be fully discussed in the chapters devoted to that subject.

Disturbances in the Cellular Storage, Assimilation, and Dispersion of Fat in the Viscera

The amount of fat in a parenchymatous organ depends on the following factors: the rate at which fat is brought to the organ by the

moderately enlarged, but if there is an associated necrosis of hepatic cells, it may be decreased in size. The color is distinctly yellow, and the intensity and uniformity of this yellow color vary with the amount of fat in the hepatic cells and the amount of blood in the intrahepatic vessels. The consistency varies with the melting point of the deposited fat. At body temperature the consistency is decreased and the tissue is friable. At room temperature and lower (after the usual refrigeration of bodies and organs) the liver is firmer than normal, but retains the friability. Microscopic examination reveals either of two characteristic appearances. In one the cytoplasm and

nucleus of the hepatic cell are collected at the periphery of the cell, and surround a single large vacuole. In the other there are numerous small vacuoles throughout the cytoplasm. In the former the nucleus and cytoplasm, aside from the displacement, are essentially normal, while in the latter degenerative changes are common.

Fat Infiltration and Fatty Degeneration. On the basis of these observations, Virchow (in the first volume of the journal now known as "Virchows Archiv") designated the former condition, which he thought was essentially a

position of fat in the liver. A few of the better known are choline deficiency, starvation, hepatotoxic agents, lipocaic deficiency, and the lipotropic hormone of the anterior pituitary gland (McHenry and Patterson).

Fatty Metamorphosis of the Kidneys, Heart, and Pancreas. The kidney in fatty metamorphosis is usually slightly enlarged, and a mottled yellow red. On cut section the pars convoluta appears as yellow bands, separated by the red or brown pars radiata. In the medulla there may be yellow streaks, indicative of a deposition of fat in the cells of Henle's loop.

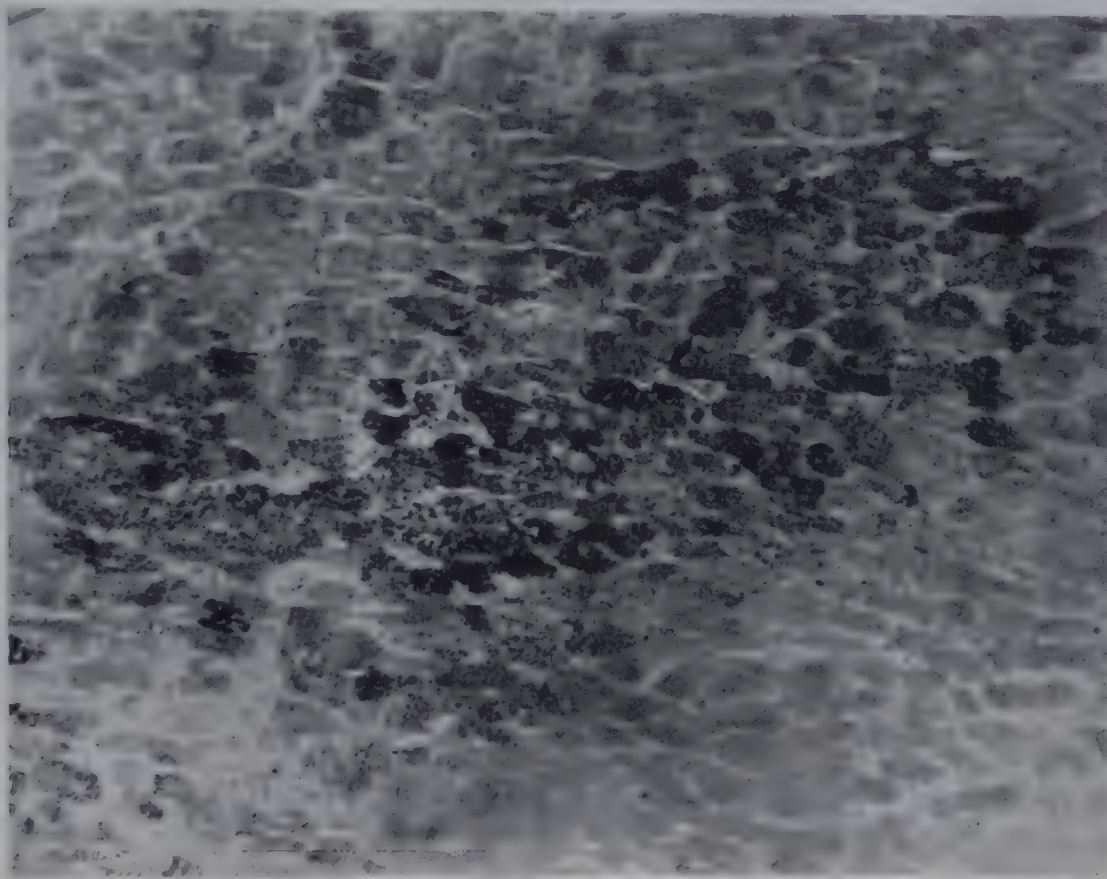


Fig. 24. Fatty metamorphosis (degeneration) of the myocardium. Stained with osmic acid.

storage of fat, as "fat infiltration"; and the latter, which he thought a degeneration of the cytoplasm with liberation of fat, he called "fatty degeneration."

Fat Transport. This concept of Virchow implied that the fat in fatty metamorphosis of the liver was derived from two different sources in infiltration and degeneration. Modern studies with fats labeled with deuterium indicate that this concept is not correct, but that the fat in all types of fatty liver is brought to the liver (Nutrition Reviews).

Lipotropic Factors. There are many factors which influence the mobilization of depot fat and the utilization of it by the liver. It follows that there are many different causes for de-

The involved cells, typically those of the proximal convoluted tubules and Henle's loop, are enlarged, and the cytoplasm is distended with numerous small vacuoles. The cytoplasm and nuclei may or may not show the changes of necrosis. In the heart the fat is not deposited uniformly but in narrow bands or in small or large foci. The bands are arranged at right angles to the long axis of the heart, and are best seen in the papillary muscles of the left ventricle, giving the characteristic "tigerling." The foci, spherical or elongated, yellow and soft, vary from 1 to 10 mm. in diameter, and are usually seen just beneath the pericardium. Both types have a similar microscopic appearance. The muscle fibers are enlarged and filled

with small vacuoles. Fatty metamorphosis of the pancreas produces little change in the gross appearance of the organ, but microscopically numerous small vacuoles are demonstrable in the secretory cells.

Chemical Analysis of the Organs in Fatty Metamorphosis. Quantitative analysis of the amount of fat in fatty metamorphosis of the liver shows that there is an appreciable increase from averages of 12 to 20 to over 25 or 30 gm. per 100 gm. of tissue. In sharp contrast are the results in fatty metamorphosis of

Causal Factors in Fatty Metamorphosis. It is evident that the causes of fatty metamorphosis fall into two categories: Agents that interfere with the cellular assimilation of fat, and agents that interfere with the state of cellular dispersion of fat. Among the former are the lipotropic factors and the latter include anoxia and toxic agents such as chloroform.

Sudden Death in Fatty Metamorphosis of the Liver. In any large autopsy service including medicolegal cases an occasional instance

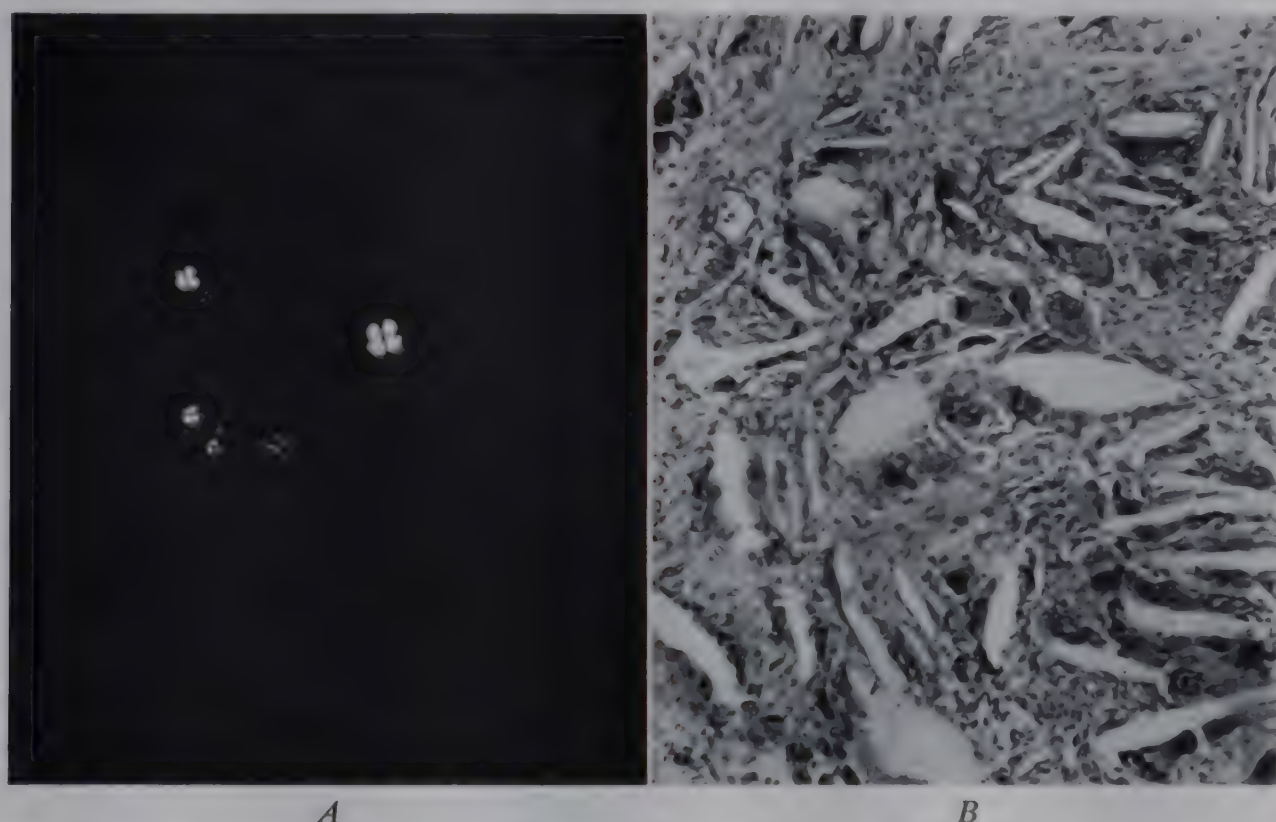


Fig. 25. *A*, Doubly refractile crystals of cholesterol esters in lipid nephrosis. Photographed with polarized light. *B*, Cholesterol crystals in the wall of a dermoid cyst of the ovary surrounded by giant cells. (Tissue by courtesy of Dr. Elson Helwig.)

the kidney, heart, and pancreas. In the experiments of Rosenfeld the extractable fat in a normal dog kidney ranged from 18.5 to 29.1 gm. per 100 gm. of tissue of the dry weight, while in intense fatty metamorphosis values of 16.9 to 22.6 were secured.

Fat Phanerosis. Manifestly the sources of the fat in fatty metamorphosis of the liver and in fatty metamorphosis of the kidneys, heart, and pancreas are not the same. In the liver the fat is transported to the organ and accumulates in it, while in the other viscera the fat exists in "masked" form and is only made visible by the pathologic process. This conversion of masked to visible fat is known as "fat phanerosis." The masked fat is probably finely emulsified or combined with amino acids and proteins. Both states are altered by the causal agents of fatty metamorphosis.

of sudden death in chronic alcoholics, with few findings except in advanced fatty metamorphosis of the liver, is encountered. It is assumed that the filling of the hepatic cells interferes with their ability to carry on certain metabolic processes, and hence death ensues (Graham).

Disturbances in the Metabolism of Ceroid

Ceroid, a greenish yellow, fluorescent, lipoidal pigment, is probably a polymer of the peroxides of unsaturated fatty acids. It is seen in the hepatic cells in experimental cirrhosis, in macrophages throughout the body, in the cortex of the adrenal, and in the ovary. In vitamin E deficiency there is an increased deposit (Popper, Gyorgy, and Goldblatt).

Disturbances in the Metabolism of Sterols

The sterols are complex, hydro-aromatic, secondary alcohols, contained in the unsaponifiable fraction of oils and fats. In animals the most important are cholesterol, vitamin D, the sex hormones, and the bile acids.

Demonstration in Tissue. The normal cholesterol and cholesterol esters are in finely emulsified form and are not demonstrable by histologic methods. In certain pathologic conditions, however, they are deposited in tissue as liquid crystals or as solid crystals. In lipid nephrosis the epithelium of the kidney contains liquid crystals of cholesterol esters, easily seen if frozen sections are examined with polarized light. Similar crystals are present in the urinary sediment, and constitute an important diagnostic feature of nephrosis. In arteriosclerosis the deposit is as fusiform crystals (esters) or as flat plates with notched corners (free) in the thickened intima. Whenever tissue undergoes necrosis, similar crystals may form, and not infrequently foreign body giant cells are present about the crystals. This is particularly true in dermoid and epidermoid cysts if the cholesterol-rich fluid comes in contact with the stroma through degeneration of the epithelial lining.

Effect of an Excess of Dietary Cholesterol. Excessive cholesterol in the diet causes a type of arteriosclerosis in the rabbit, and in many species results in fatty metamorphosis of the liver. There is no clear evidence that the same is true in man.

Disturbances in the Metabolism of Phospholipids

The phospholipids are a group of fat soluble compounds containing glycerol, phosphoric acid, fatty acids, and a nitrogenous base. There are three nitrogenous bases, and these form the basis for classification into the lecithins, which contain the base choline, the cephalins, which contain the base amino-ethyl alcohol, and the sphingomyelins, which contain the base sphingosine. The latter are closely related to the cerebrosides, which contain the same base but not phosphoric acid. The fatty acids in all are highly unsaturated.

Little is known concerning the relation of phospholipids to disease. They are necessary

for the utilization of fat by the liver, and in Niemann-Pick disease phospholipid accumulates in reticulo-endothelial cells. In general there is a constant ratio between phospholipid and cholesterol in the blood.

Disturbances in the Metabolism of Cerebrosides

The cerebrosides are a group of compounds which on hydrolysis yield sphingosine, galactose, and fatty acids. They do not contain phosphorus or glycerol, and thereby differ from the phospholipids. There are two important cerebrosides: kersin, yielding lignoceric acid, and phrenosin, yielding cerebronic acid. When viewed in frozen sections with polarized light and a selenium plate, the crystals of each have a characteristic color pattern and can be distinguished. Other less well known cerebrosides are nervon and cerebrin.

Cerebrosides are found in all tissues, but are most abundant in nervous tissue. Their function is not well defined, and their relation to disease is little known. A leptomenigeal cyst, the fluid of which contained 72 per cent cerebroside, has been reported (Troop and Eckardt). Decreases in the cerebroside content of the red blood cells in pernicious anemia (Kirk), and of the nerves in patients with arteriosclerosis and diabetes (Randall), have been observed. If an excess of cerebroside is fed, it is stored in the liver and other tissues, and gradually oxidized over a period of weeks or months. Gaucher's disease, in which there is an accumulation of cerebroside in reticulo-endothelial cells, is discussed in the following section.

Disturbances in the Metabolism of Lipids Associated with the Accumulation of Lipids in Reticulo-endothelial Cells

Under certain poorly understood conditions large amounts of lipid accumulate in reticulo-endothelial cells, and occasionally in other cells. It is customary to divide these conditions into several types on the basis of the chemical nature of the lipid. Subtypes are recognized on the basis of the organ or organs affected and the presence or absence of excessive amounts of lipid in the blood (Jaffe; Thannhauser and Schmidt).

- I. Cerebroside lipidosis—Gaucher's disease
- II. Sphingomyelin lipidosis—Niemann-Pick disease
- III. Ganglioside lipidosis—Amaurotic family idiocy
- IV. Cholesterol lipidosis—Xanthomatosis
 - A. Primary including Hand-Schüller-Christian disease
 - B. Secondary
 - C. Localized xanthomatosis

Pathogenesis of Primary Lipid Histiocytosis. When these remarkable conditions were first observed, it was thought that the accumulation of lipid represented an abnormal storage, hence the designation of the entire group as storage diseases. With more precise study attention has been increasingly focused on the idea that the basic defect is in the metabolism of the reticulo-endothelial cells.

GAUCHER'S DISEASE

This type of lipid histiocytosis is a familial condition having its onset in infancy or in childhood, and is characterized by the deposit of the cerebroside kersin or a closely related cerebroglucoside in many tissues, notably in the liver, spleen, lymph nodes, and bone marrow.

The spleen is enormously enlarged and may occupy more than half the abdomen. On section the architecture appears obscure, and the pulp is seen to be uniformly gray and firm. The liver is moderately enlarged, and throughout the substance there may be small yellowish gray flecks. The lymph nodes are enlarged and gray. In the bone the trabeculae are inconspicuous, and the cortex is thin. The red or yellow marrow is replaced by firm, gray, opaque tissue.

The outstanding microscopic feature is the presence of the Gaucher cell. This cell is from 20 to 40 microns in diameter, spherical or ovoid, and is found in solid clumps or in pseudo-acinar arrangement. The nuclei are small, often placed peripherally, and they have a fine chromatin structure with distinct nucleoli. Multinucleated cells are common, and the nuclei are frequently shrunken and pyknotic. Mitoses are rarely seen. The cytoplasm is abundant and contains numerous fine, interlacing, branched, wavy fibrils. Between the fibrils is the characteristic lipid deposit that is not soluble in the usual fat

solvents. It stains light yellow or not at all with sudan III. With Mallory's aniline blue it is a light blue or bluish gray. Occasional granules of hemosiderin are observed in the cytoplasm. Between the cells there is a delicate argentaffin reticulum. It is believed that the Gaucher cell is derived from the reticulum cell and not from the endothelium. Hence in the earlier stages it is found in the interstitium of an organ, but later may migrate into the capillaries.

Although the onset of Gaucher's disease is usually in childhood, most patients live into early adulthood. A few die in the first few years of life of the infantile form. The course is rapid and many tissues in addition to the spleen, liver, lymph nodes, and bone marrow are affected—tonsils, thymus, adrenals, intestine, and lungs. There is frequently mental retardation; and a peculiar atrophy of the ganglion cells of the cortex without neurophagia, cellular infiltration, or deposit of Gaucher cells may be seen microscopically (Aballi and Kato).

In adults there is a characteristic proliferation of the conjunctiva—pinguecula—and a brown pigmentation of the skin. The average duration of life is twenty years, and death usually results from some intercurrent disease. The moderate anemia, leukopenia, and thrombocytopenia have been attributed to the replacement of the marrow and to hyperfunction of the spleen. The latter idea is supported by the observation that splenectomy in some instances is followed by improvement. The diagnosis is easily established by puncture biopsy of the bone marrow, spleen, or lymph nodes. Gaucher cells are only rarely found in the peripheral blood. Occasionally the involvement of the bone marrow is extensive, or takes the form of focal tumors, so that there are pain, deformities such as kyphosis, and spontaneous fracture. This is known as the osseous form of Gaucher's disease.

NIEMANN-PICK DISEASE

This is a rapidly progressive and fatal disease of childhood. In advanced cases there is extreme emaciation, distention of the abdomen, and a brownish gray pigmentation of the skin. The liver and spleen are greatly enlarged. The capsules are smooth and not thickened. The cut surfaces are yellowish gray and homogeneous. The reticulo-endothelial cells,

notably in the liver and spleen, but to a less extent in all tissues of the body, are filled with vacuoles. Other sites of localization are the adrenal cortex, the septa and alveoli of the lung, and the intima of small and large arteries. The typical cell is 20 to 70 microns in diameter, with a small chromatic nucleus and a cytoplasm that is represented only by thin septa that separate small and large round vacuoles. After mordanting with chromates the contained lipid stains with sudan III and with Nile blue sulfate. As in Gaucher's disease it is believed that the Niemann-Pick cell is

AMAUROTIC FAMILY IDIOCY

This familial condition, also known as Tay-Sachs disease, is characterized clinically by idiocy and blindness. The brain may show no gross changes, but in most instances the convolutions are atrophic and firm, and the sulci broadened and deepened. The ventricles are dilated. Pathologic lesions of the ganglion cells of all parts of the brain may be seen microscopically. The cells and the dendrites are swollen, and they assume varied irregular shapes. The nuclei are well preserved and displaced to the side of the cell. The Nissl bodies

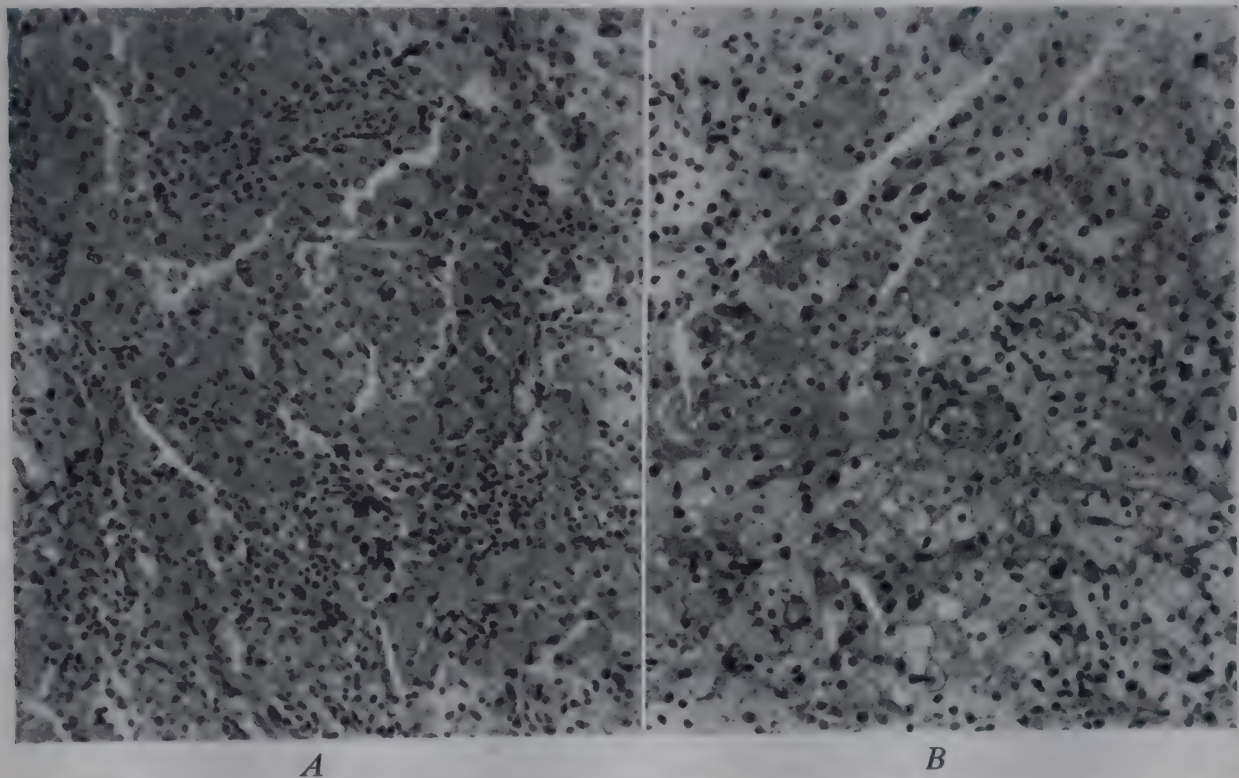


Fig. 26. *A*, Large pale cells in the spleen in Gaucher's disease. *B*, Bone marrow of rib in Hand-Schüller-Christian disease.

derived principally from the reticulum and to a less extent from endothelial cells and tissue histiocytes (Bloom). On chemical analysis, from 6 to 14 per cent of the dry weight of the spleen is phosphatide. It was originally thought that this was lecithin, but it has now been proved that the greater part is sphingomyelin.

Children with Niemann-Pick disease appear normal at birth and for some weeks thereafter, but before the end of the first year retardation of physical and mental development is noted. The enlargement of the spleen and liver, with consequent distention of the abdomen, is the outstanding sign. Over 70 per cent of patients are girls, and there is a definite familial and racial tendency; predilection for those of Jewish ancestry is even more striking than in Gaucher's disease.

are reduced in size and number, and are found only about the nucleus. The cytoplasm is granular, and stains basophilically. The neurofibrillae are intact. Associated with the cellular changes there are extensive demyelination and proliferation of astrocytes. There is no evidence of inflammation (Rothstein and Welt).

Pathologic changes in the other viscera except the eye are limited and inconstant. Death usually results from an intercurrent infection such as pneumonia. In the eye there is degeneration of the ganglion cells of the retina in the region of the macula so that the choroid is exposed and seen with the ophthalmoscope as the pathognomonic cherry red spot.

The onset is usually at four to six months of age, and the average duration of life is

eighteen months. There is both a familial and a racial factor, since the disease is rare in any but those of Jewish extraction. The degeneration of cerebral ganglion cells leads to progressive muscular weakness and loss of volitional control. In the late stages there are conspicuous mental retardation and other less easily explained symptoms such as hyperacusis and emotional outbreaks. The degeneration of the retina and of the optic nerve is the basis of the blindness.

The lipid present is ganglioside, a type present in normal brain, but greatly increased

tendons, bile ducts, endocardium, and blood vessels. If the cholesterol level in the blood is normal, deposits are more common in the skin, bones, lungs, and hematopoietic organs. In the lungs and liver, late stages are manifested by a progressive fibrosis. According to the gross appearance of the lesion in the skin, special terms such as "xanthoma tuberosum," "xanthoma planum," and "xanthoma disseminatum" have been used. In secondary or symptomatic xanthomatosis there are isolated collections of foam cells in the skin, spleen, liver, and lymph nodes. These are most com-

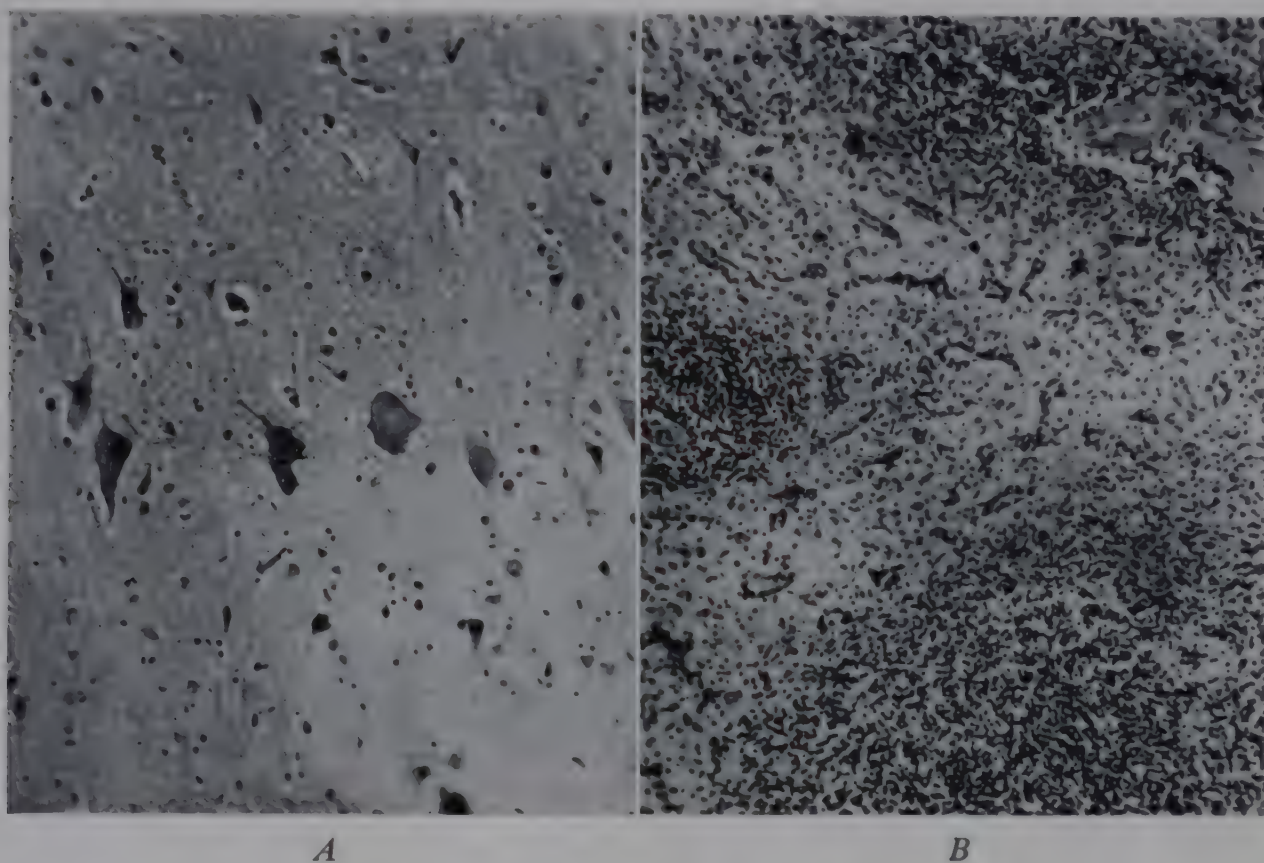


Fig. 27. *A*, Swollen nerve cells in the brain in amaurotic family idiocy. *B*, Fat-laden macrophages in the spleen in severe untreated diabetes mellitus.

in this disease. There is probably no relation between amaurotic family idiocy and Niemann-Pick disease.

CHOLESTEROL LIPIDOSIS—XANTHOMATOSIS

From the anatomic standpoint it is convenient to recognize three conditions: xanthomatosis, Hand-Schüller-Christian disease, and eosinophilic granuloma of bone.

Xanthomatosis. In general, xanthomatosis is the deposit of cholesterol in cells in the form of tumor nodules (primary) or in individual cells of a preexistent disease (secondary). In some patients with the primary type there is a hypercholesterolemia, while in others the serum cholesterol is normal. The most frequent sites of xanthomas with hypercholesterolemia are the skin, tendon sheaths and

mon in diabetes mellitus, and are described under the name "xanthoma diabeticorum" (p. 868). Occasionally a similar lesion of the spleen and lymph nodes is seen in patients without diabetes—large cell hyperplasia of Schultze.

Pathologic Anatomy. The pathologic changes are essentially the same in all types. There are yellow, circumscribed but not encapsulated, moderately firm tumors. Microscopically the normal elements are observed to be separated or destroyed by the presence of numerous large foam cells. The cytoplasm contains small vacuoles. The nuclei are small and hyperchromatic. Mitoses are not seen. With degeneration of the foam cells fat is liberated and hydrolyzed. The crystals of free fatty acid stimulate the formation of foreign

body giant cells and the growth of fibrous tissue. Deposits of hemosiderin in phagocytes are frequently observed.

Xanthomatous Changes in Tumors. In certain true neoplasms, especially in the fibroma, focal areas of xanthomatosis are observed. These should be regarded as a degenerative or metabolic change in the tumor cells, and should not be confused with xanthomas or xanthomatosis, which are not neoplasms.

Hand-Schüller-Christian Disease. The gross and microscopic changes in this type of cholesterol lipidosis, first defined as a clinical

alveolar processes for the loosening of the teeth. In the brain the oligodendroglia and the microglia swell and the cytoplasm becomes foamy. Other common sites are the skin, lungs, liver, spleen, lymph nodes, pancreas, mediastinum, and retroperitoneal tissues. In all of these there are progressive fibrosis and impairment of the function of the organ. In the lung this results in dyspnea, and in the liver and pancreas in conversion of the organ to the appearance of cirrhosis. Fibrosis in the lung may interfere with the circulation through that organ, with consequent hypertrophy of

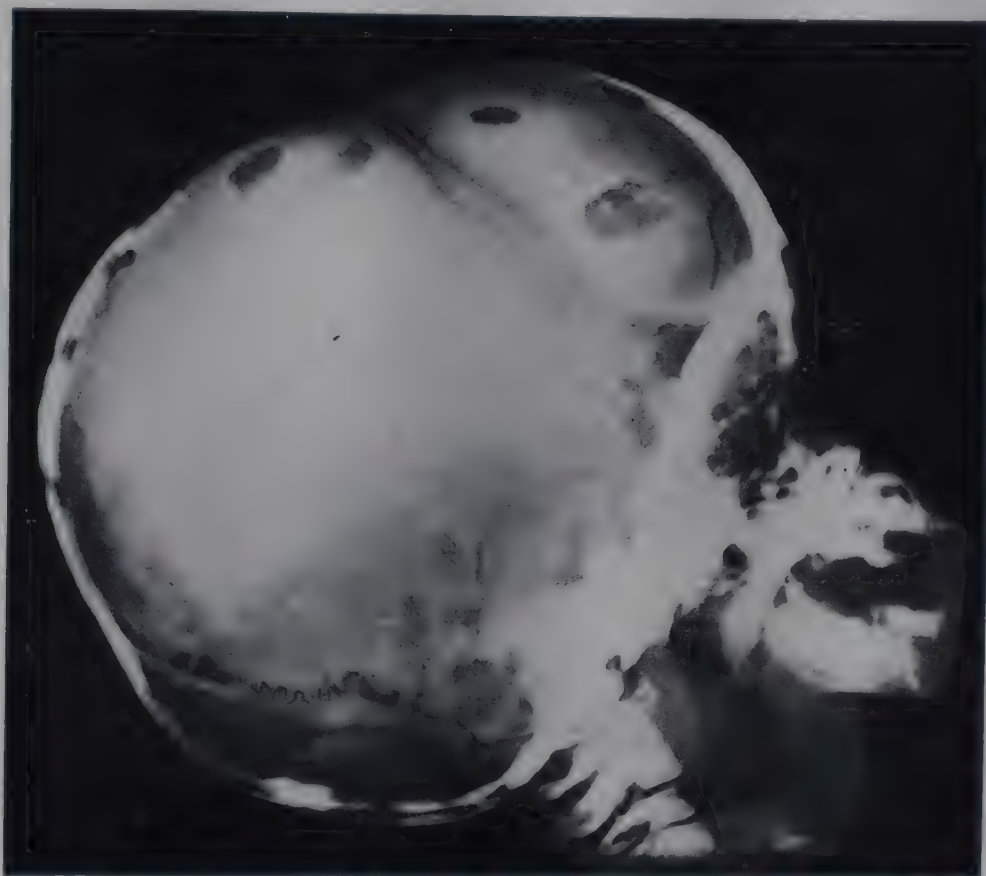


Fig. 28. Focal resorption of the bone of the skull in Hand-Schüller-Christian disease. (Radiograph by courtesy of Dr. Sherwood Moore, M. I. R. 130986.)

syndrome by Christian, are similar to or identical with those in xanthomatosis, except that there are certain sites of predilection and that there is a tendency to fibrous replacement of the foam cells. In over 85 per cent of all instances there are focal deposits in the tissue about the skull. An accumulation in the region of the sella turcica leads to disturbance in hypophyseal function (diabetes insipidus) and to filling of the posterior part of the orbit with forward pressure on the eyeball (exophthalmos). The nodules in the dura grow outward and bring about resorption of the bone in a sharply punched out area clearly seen on the x-ray plate (Fig. 28). Deposits in the temporal bone and middle ear are responsible for deafness, and deposits in the

the right ventricle. The lesions in the skin are variable, but usually sufficiently definite to warrant a diagnosis (Lane and Smith). Less commonly there are isolated nodules in the short bones of the hands and feet.

The foam cell is derived from the tissue histiocyte. Between the foam cells there are variable numbers of polymorphonuclear leukocytes, plasma cells, eosinophilic leukocytes, and fibroblasts. With increasing age of the lesions there is increasing proliferation of the fibrous tissue and deposit of collagen. Chemical analysis of the tissues reveals a high content of cholesterol, cholesterol esters, neutral fat, and a phosphatide, probably lecithin. Under polarized light the lipid is seen to be anisotropic in large part.

Incidence. The usual age of onset is the second or third year of life, and the course averages one to four years. Boys are more frequently affected than girls. There is no evidence of a familiar factor. In some patients the nodules are extremely radiosensitive.

Nature. Although Hand-Schüller-Christian disease is included under the lipoid histiocytes, there is increasing evidence that it is primarily a granulomatous type of inflammation.

Eosinophilic Granuloma of Bone. This is a solitary or multiple lesion of bone in children and young adults. The essential feature is a sheet-like accumulation of histiocytes and reticulum cells free of fat infiltrated with eosinophilic leukocytes and a few multinucleated cells. There is associated resorption of bone so the lesion is radiolucent (Jaffe and Lichtenstein).

Nonlipid Reticulo-endotheliosis—Letterer-Siwe Disease. Rarely cases are observed that have many of the features of a lipid histiocytosis except that there is no deposit of lipid. There is the same proliferation and accumulation of large histiocytes diffusely and focally in the tissues. It is possible that the two conditions are related, but further study is needed (Foot and Olcott).

Disturbances in the Metabolism of Lipochromes

Lipochromes are diffuse or finely dispersed yellow pigments found in tissues in association with fat. They are soluble in fat solvents, do not stain with the fat stains, bleach readily when exposed to oxidizing agents, become crystalline on treatment with alcoholic potassium hydroxide, and are present normally in the adrenal cortex, corpus luteum, liver, spleen, fat tissue, and skin. Increased amounts are demonstrable in the intimal plaques of arteriosclerosis, in xanthomas, in all tissues following ingestion of large quantities of lipochrome, and in association with lipemia.

The lipochromes found in animals consist chiefly of carotene and xanthophyll, and are entirely exogenous in origin—that is, they are ingested in the food and not formed by animal tissues (Connor).

Carotenemia. Following the ingestion of large amounts of carotene, as in a diet rich in carrots, the serum and occasionally the skin

take on a yellow coloration. So far as can be determined there are no related or significant physiologic or anatomic changes (Head and Johnson).

Irreversible Changes in Intracellular Fat—Fat Necrosis

In the lesion known as fat necrosis the neutral fats in the cells of adipose tissue are split to fatty acids and glycerol. The most common form is pancreatic fat necrosis, in which small, white, opaque, pasty foci, 1 to 3 mm. in diameter, are seen in the peripancreatic, mesenteric, and omental fat. The nuclei and cytoplasm of the fat cells are lost and the central vacuole is replaced by a finely granular acidophilic debris. Occasional spindle-shaped spaces are observed, and in properly prepared frozen sections fatty acids can be identified. There may be an associated slight hemorrhage. An interesting variant of fat necrosis is that of stored fat in hepatic cells. This occurs in conditions bringing about occlusion of the ampulla of Vater and probably forceful retrojection of pancreatic juices into the intrahepatic bile ducts (Schiller).

Chemical Aspects. Serial chemical studies show that the initial change is hydrolysis of the neutral fat. The glycerol is freely miscible with the body fluids and diffuses, while the fatty acids combine with base to form soaps. It is these soaps that appear as the pasty white foci.

Pathogenesis. Pancreatic fat necrosis is seen in any condition in which pancreatic juice escapes from the ducts within the gland. This occurs in trauma and acute inflammations, in acute hemorrhagic necrosis, and in debilitating conditions of older people in which death comes on slowly. It is probable that the escaping trypsinogen activated by the tissue fluids causes necrosis of the cells and exposes the contained fat to the action of lipase. In experimental animals grossly visible fat necrosis appears in three to five hours, and in eight to ten days there is complete healing.

Fat Necrosis Other than Pancreatic. In addition to the fat necrosis related to the pancreas similar lesions are seen in traumatic fat necrosis (p. 484) and in sclerema neonatorum (p. 579), which conditions are discussed in other chapters.

Postmortem Changes in Fat— Adipocere

If an unembalmed body is buried in wet ground, after some months the subcutaneous tissues and muscle are converted into waxlike structures. It was originally considered that this represented the postmortem conversion of protein to fat. However, careful study has shown that the process is more one of de-

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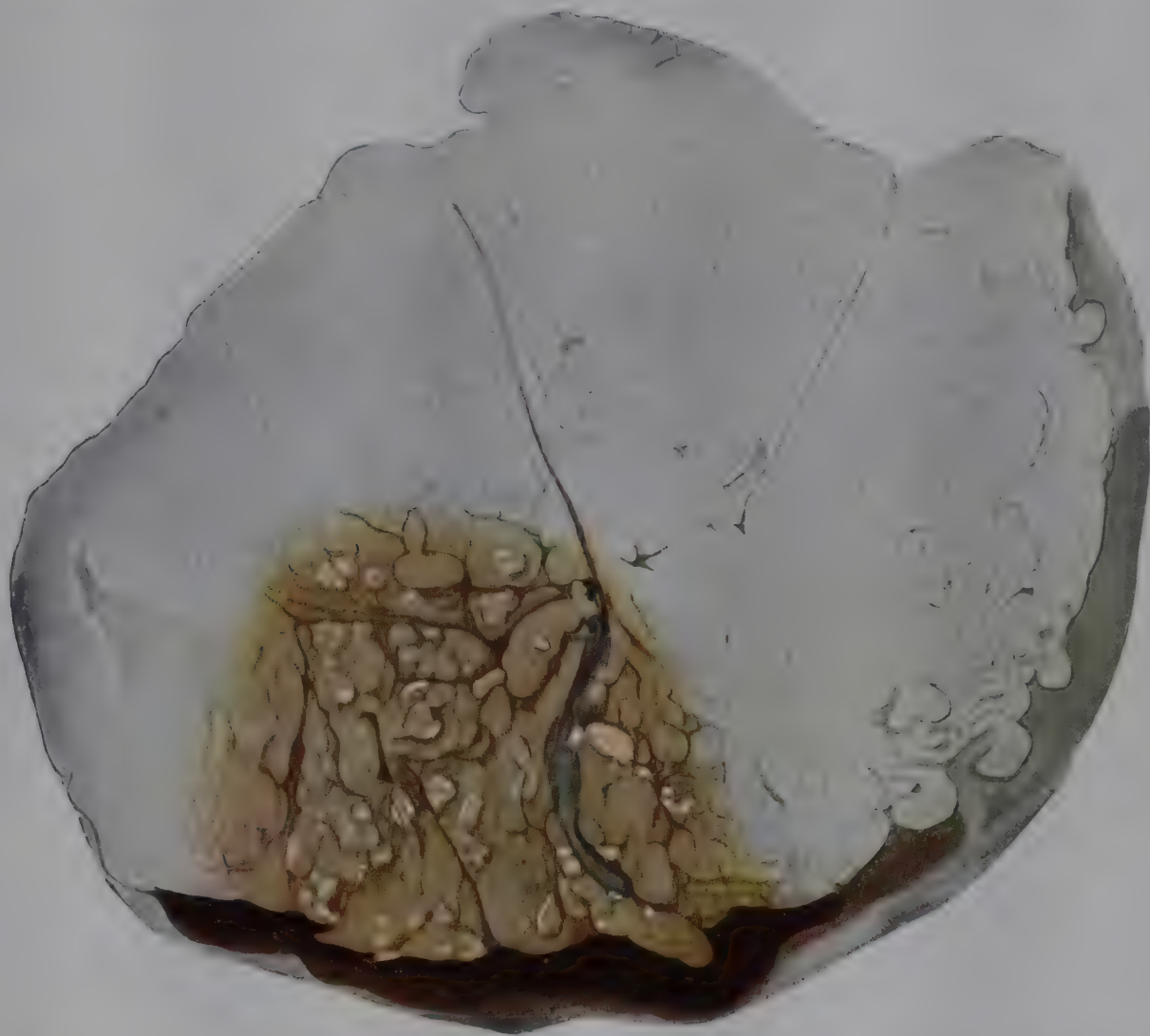


Fig. 29. Pancreatic fat necrosis in the omentum. (MacCallum: *Textbook of Pathology*.)

struction of protein and migration of liquid fat in the following manner. In all normal fat there is a small amount of free fatty acid. If the proteins undergo decomposition, ammonia is released, which combines with the fatty acid to form the ammonium soap. According to the law of mass action, more free fatty acid will be split from the neutral fat, and eventually all of the fat will be converted to the soluble ammonium, sodium, and potassium soaps. These are free to diffuse throughout the tissues, and gradually are converted into the insoluble soaps of calcium. It should be noted that this process does not occur in the viscera.

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VI

Disturbances in the Metabolism of Minerals

Although the minerals constitute only a small part of the body tissues and fluids, they enter into many important physiologic processes. There are seven principal essential minerals: calcium, magnesium, sodium, potassium, sulfur, phosphorus, and chlorine. In addition there are six essential "trace" elements: iron, copper, iodine, manganese, cobalt, and zinc. It is possible, but not proven, that fluorine, aluminum, and boron are necessary.

Disturbance in the Metabolism of Sodium and Chlorine

Sodium forms the largest part of the total base of the body fluids, and in union with chloride and bicarbonate functions to maintain osmotic balance and ionic equilibrium.

Requirements and Turnover. Man consumes from 3 to 6 gm. of sodium and from 4 to 7 gm. of chlorine a day, most of which in the United States is derived from the salt used in seasoning. When the body is in salt balance about 10 gm. of sodium chloride is lost in the sweat and urine each day.

Effects of a Deficiency. In man there are no known conditions in which there is a selective deficiency of sodium or chloride, and the effects of a single deficiency can be demonstrated only in experimental animals.

Deficiency of Sodium. After rats are fed a diet extremely low in sodium, the ducts of the meibomian glands become dilated and the palpebral conjunctiva is lined with keratinized epithelium. The cornea is infiltrated with leukocytes, vascularized, and covered with keratinized epithelium. The bones cease to grow, and spermatogenesis and oogenesis are suppressed, probably as the result of inanition (Follis, Orent-Keiles, and McCollum).

Deficiency of Chlorine. Growth is retarded after ninety days in rats fed a low chlorine

diet (Orent-Keiles, Robinson, and McCollum). In man a severe alkalosis is induced. There is no change in renal function (Kirsner, Palmer, and Knowlton).

Deficiency of Sodium Chloride. In man deficiencies of salt result from excessive loss, as in sweating, vomiting, and diarrhea, and from restricted intake, as in persons stranded in lifeboats on the ocean (Marriott). In total starvation the animal organism retains salt most tenaciously. Within ten days the excretion of sodium falls to 0.1 gm. or less per day, and when salt is fed, some time may elapse before the excretion rises. In a dry, hot environment as much as 15 gm. of salt may be lost in the sweat in twenty-four hours (Dill, Jones, Edwards, and Oberg). Dairy cows deprived of salt for some weeks or months have loss of appetite, lusterless eyes, a rough coat, and a rapid decline in weight and yield of milk. Collapse and death are likely to be sudden and to follow calving. There is some evidence that a deficiency of salt unfavorably influences carbohydrate metabolism. In adrenal insufficiency there is a decrease of serum sodium. In chronic hypochloremia there may be varied psychosomatic disturbances.

The excessive loss of fluid in diarrhea and vomiting leads to serious alterations in the chemical constituents of the blood and extracellular fluids. Plasma proteins are concentrated and may reach values of 8 or 9 gm. per 100 cc. (Bridge, Cohen, and Scott). The base bicarbonate is much reduced by actual loss in the intestinal secretion. As the result of vomiting, chlorides are lost, and there is no bicarbonate to take the place of the chlorides, so that the entire base side of the acid-base balance is decreased. The loss of fluids in vomitus and diarrheal stools induces dehydration and excessive formation of lactic acid,

adding to the acidosis. The oliguria is responsible for retention of phosphates and non-protein nitrogen.

Effects of an Excess. In general, animals will not consume food or drink with a salt content above 1 to 2 per cent, but a tolerance up to 3 or 4 per cent can be obtained by a gradual increase. Excessive ingestion of salt

Disturbances in the Metabolism of Potassium

Potassium is the principal intracellular cation and the concentration in cells is higher than in serum and intercellular fluid.

Requirement. It is estimated that the adult requires 0.06 gm. of potassium per kilogram

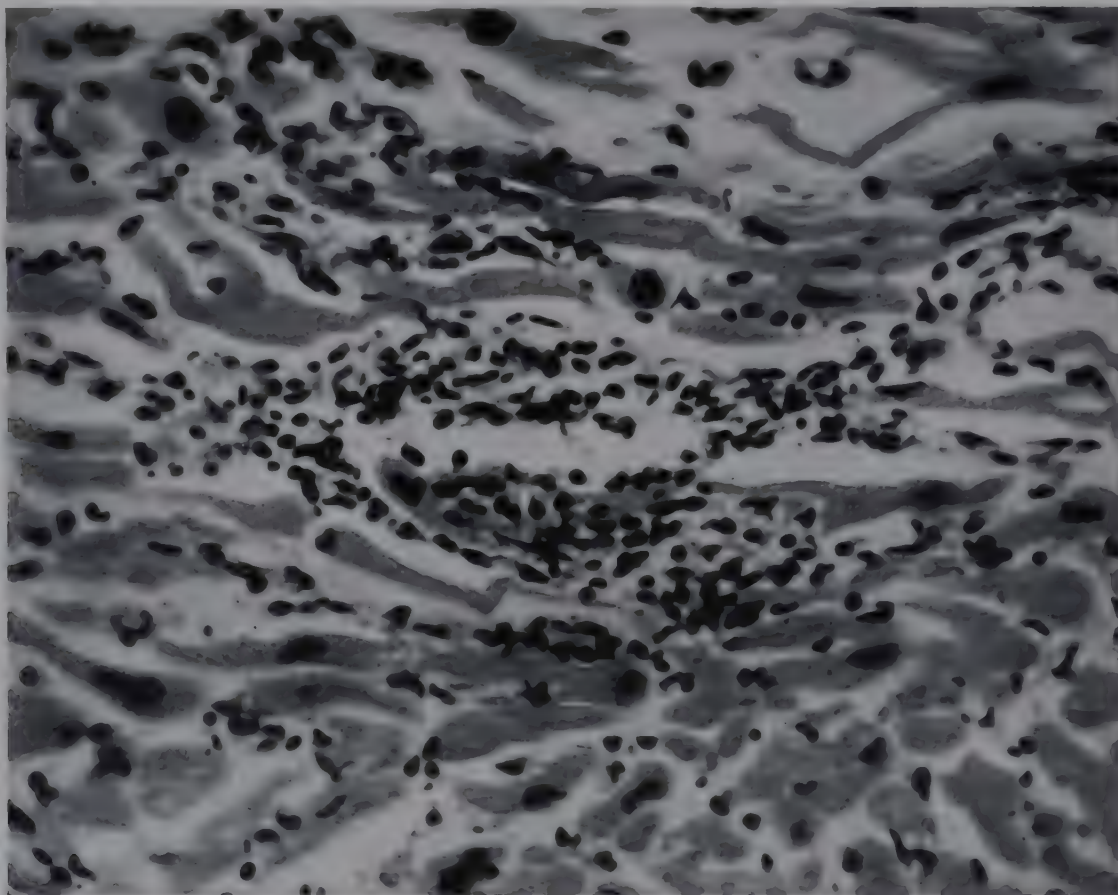


Fig. 30. Focus of necrosis in myocardium in potassium deficiency. From a patient with Addison's disease treated with large amounts of desoxycorticosterone acetate.

as by drinking sea water leads to cellular dehydration with respiratory failure (Elkiston and Winkler).

Retention of Chlorides in Infectious Diseases. In most infectious diseases, but notably in lobar pneumonia, sodium chloride is retained in the extravascular fluids, with a corresponding decrease of the serum chloride and the urinary chloride. During recovery the salt is released and excreted in the sweat and urine (Sunderman).

Acute Salt Poisoning. If animals deprived of salt are allowed to satisfy their craving, as much as a pound or more may be rapidly consumed and toxic effects may ensue. The animals show extreme thirst, depression, and abdominal pain, and frequently collapse and die. The anatomic changes are congestion and edema of the gastro-intestinal tract and of the brain.

of body weight per day, and the child 0.07 gm. Ordinary diets furnish 2 to 4 gm.

Effects of a Deficiency. Because of the ubiquitous occurrence of potassium in food-stuffs it is unlikely that man or animals ever suffer from the effects of a dietary deficiency.

Experimental Dietary Deficiency. In animals maintained experimentally on a low potassium diet there is degeneration of the epithelium of the proximal convoluted tubules of the kidney. The heart muscle is soft, mottled, and grayish red, and the cavities are dilated. Throughout the myocardium, involving both the ventricles and the atria, there are small foci of necrosis with slight infiltration with lymphocytes and mononuclear cells. In animals deficient also in thiamine this lesion does not occur (Follis).

Hypopotassemia in Addison's Disease. We have studied the tissues of a young woman

who died after the administration of large amounts of desoxycorticosterone acetate, given during a crisis of Addison's disease (Goodof and McBryde). There were lesions in the heart (see Fig. 30) and kidneys, identical with those found in potassium-deficient animals and in cats and rats given excessive amounts of desoxycorticosterone acetate (Darrow and Miller).

Hypopotassemia in Diabetes. If in the treatment of diabetic acidosis potassium is used in glycogenesis and lost by diuresis, symptoms of hypopotassemia may be observed in the form of paralysis (Holler).

Familial Periodic Paralysis. In this usually hereditary condition there are recurrent attacks of weakness or paralysis of the somatic muscles, spaced days or months apart, and lasting a few hours or days (Oliver, Ziegler, and McQuarrie). With the onset of paralysis there is a rapid shift of extracellular potassium to the intracellular phase with a consequent decrease of the level of serum potassium. The administration of potassium salts leads to rapid recovery indicating that the hypopotassemia is the cause of the paralysis (Danowski, Elkinton, Burrows, and Winkler). Dogs on a potassium-deficient diet develop paralysis.

Effects of an Excess. It is not possible to increase the concentration of potassium in the body fluids by ingestion of excessive amounts except for temporary periods, but in uremia, intestinal obstruction (Scudder, Zwermer, and Whipple), and in Addison's disease there is a definite hyperpotassemia. In all of these conditions there are electrocardiographic changes indicative of myocardial damage (Keith, Burchell, and Bagenstoss).

Disturbances in the Metabolism of Calcium

The adult human body contains 1400 to 2000 gm. of calcium, or 2 per cent of the body weight. About 99 per cent is in the bones. The remainder is in the ionic state or bound to protein and is of fundamental importance in the physiologic activity of nerve, muscle, and heart, in the clotting of blood, and in the maintenance of membrane equilibrium.

Requirements and Absorption. The daily requirements are: 0.8 gm. for adults, 1.0 to 1.4 gm. for children, and 1.5 to 2.0 gm. dur-

ing pregnancy and lactation. The rate of absorption from the intestine is influenced by the composition of the diet. A high protein diet increases the absorption, while the presence of phytic acid and oxalates depresses absorption.

Turnover and Control. Serum normally contains 9 to 11.5 mg. of calcium per 100 cc. This calcium is in at least three forms: (1) about 40 per cent bound to plasma protein, with the remaining 60 per cent in diffusible or ionizable form, of which (2) another 40 per cent is under the control of the parathyroids, and (3) 20 per cent is free. If the serum calcium is increased there is increased excretion, largely through the colon, and if the serum calcium is decreased the parathyroid glands are activated and the secretion of parathormone results in the mobilization of stored calcium in the bones—a process known as *halisteresis*. Further, the absorption and utilization of calcium is influenced by vitamin D (see the section on rickets, p. 549).

Effects of a Deficiency. A deficiency of calcium for normal metabolism may result from dietary lack, defective absorption, deficiency of vitamin D, decrease of plasma protein, increased excretion, or a disturbance in the parathyroid glands.

Dietary Deficiency. In rats on diets deficient in calcium, there are retardation of growth, decreased sensitivity and reactivity, paralysis of the hind legs, fall of serum calcium to 5 mg. but no tetany, and death in 60 per cent of animals within twenty-three weeks. Anatomic changes are widespread hemorrhage, especially prominent in the central nervous system, and osteoporosis (Boelter and Greenburg).

Defective Absorption. Factors influencing absorption of calcium are not well understood, but experimental studies indicate that the acidic gastric juice is essential for absorption. The osteoporosis common to older people may be related to the atrophy of the gastric mucosa and the achlorhydria which are also frequent changes of increasing age.

Ratio of Dietary Calcium and Phosphorus. The calcium phosphate of bone is in equilibrium with the calcium and phosphorus of the body fluids, which in turn are in equilibrium with the minerals in the lumen of the intestine. It follows that the presence of an abnormal

ratio of calcium to phosphorus in the intestine will result in increased excretion of both elements, and demineralization of the bones.

Influence of the Parathyroids, Tetany. In all conditions such as rickets, osteomalacia, and chronic renal insufficiency, in which there is a decrease in the ionized serum calcium, there is a hyperplasia of the parathyroid glands. On the other hand removal or pathologic destruction of the glands results in a decrease in the serum calcium, and usually in the appearance of the clinical syndrome,

into the lumen. Injection of excessive amounts of parathormone produces the same alterations with death in twenty-four hours. Chronic hypercalcemia is related to long-continued hyperfunction of the parathyroid glands and to destructive lesions of the bones. The morphologic expression is metastatic calcification.

Pathologic Calcification. Pathologic calcification by definition includes all deposits of calcium in the soft tissues, and the formation of concrements* of calcium salts in the secretory and excretory ducts of the body. Morpho-



A

B

Fig. 31. *A*, Calcification and ossification in a myoma of the uterus. (Tissue by courtesy of Dr. Elson Helwig.) *B*, Calcification of myocardial fibers. (Tissue by courtesy of Captain Ira Gore, A.U.S.)

tetany. This syndrome is characterized by hyperirritability of the nervous system, manifested by galvanic and mechanical hyperexcitability and a tendency to clonic and tonic spasms (typically carpopedal) and general convulsions. The basic biochemical lesion seems to be a disturbance in the ratio of sodium plus potassium to ionic calcium plus magnesium. It is thus possible to have either calcium or magnesium tetany.

Effects of an Excess. It is difficult to raise the concentration of serum calcium by ingestion or injection, except for short periods. However, continuous intravenous administration of large amounts of calcium and phosphate brings about the morphologic changes of acute hypercalcemia—intense congestion of the stomach and intestine, petechiae in the mucosa, and parenchymatous hemorrhage

logic manifestations of pathologic calcification may be divided into five categories: (1) dystrophic calcification, (2) calcinosis, (3) metastatic calcification, (4) calcification in the vascular system, and (5) the formation of concrements. Because of the complexity of the last two, they are discussed in other chapters (see the sections on arteriosclerosis, calcification of the valvular rings, urolithiasis, cholelithiasis, pancreatic calculi, and salivary calculi).

Identification of Calcium in Tissues and Chemical Composition of the Deposit. Chem-

* The use of the various words for spherical, solid masses in the hollow viscera of the body is frequently misunderstood. The correct use is illustrated in the following sentence: "The *concretion* of protein and other substances forms a *concrement*, which, if infiltrated with calcium salts, is a *calculus*."

ical analysis of all types of pathologic calcification reveals calcium and phosphate in large amounts, magnesium and carbonate in small amounts, and traces of alkali salts, iron, and silica. The ratio of calcium to phosphorus varies from 1.96 to 2.25. The percentage of carbonate is 10 to 15 per cent, with the higher values in the older lesions. In undecalcified sections the deposits stain intensely with hematoxylin because of the associated deposit of iron.

Dystrophic Calcification. This is the term applied to deposits in dead or dying tissue.

to the abnormal deposition of calcium salts in the skin, subcutaneous tissues, muscles, and tendons of the body. Two types are usually recognized: *calcinosis circumscripta*, in which the deposits are limited to the skin and subcutaneous tissues; and *calcinosis universalis*, in which the muscles and tendons are also involved.

The lesions of the skin and subcutaneous tissues are readily palpated and are clearly visible in roentgenograms. In many, particularly those over the great joints, there is ulceration of the skin, and secondary infec-

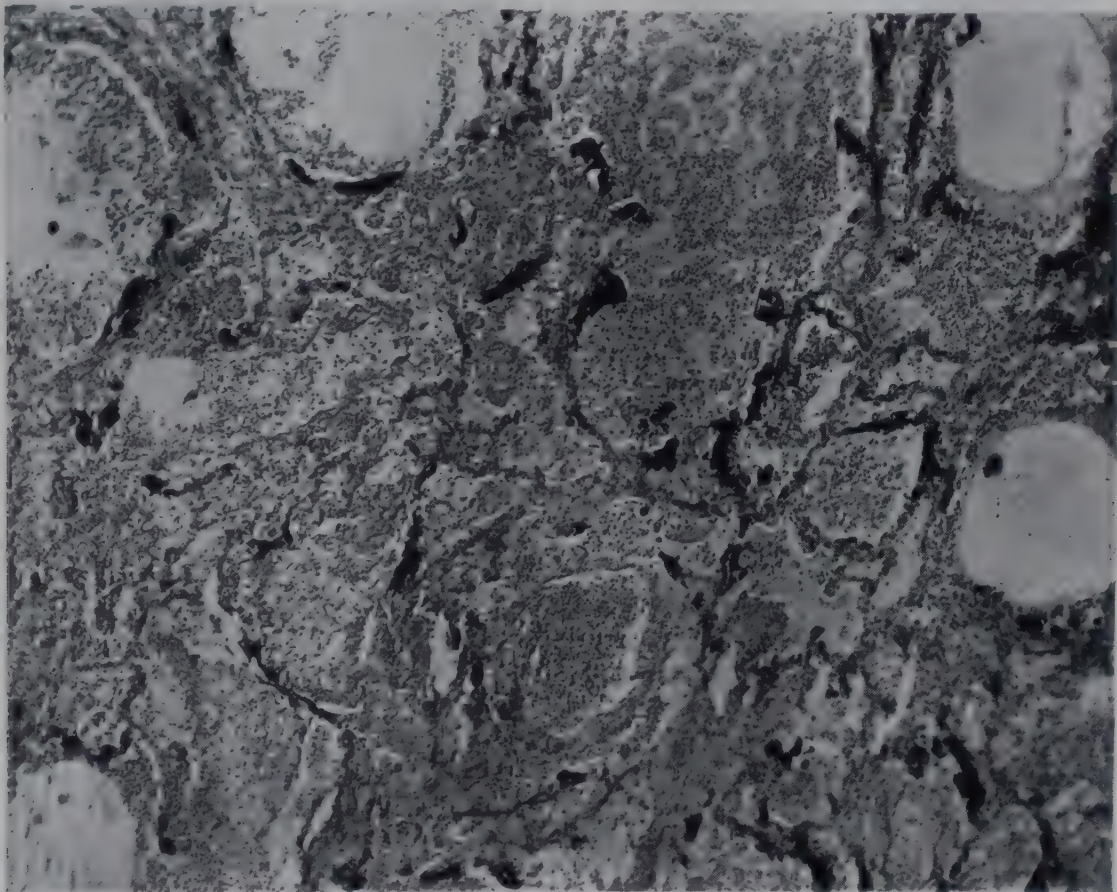


Fig. 32. Metastatic calcification of lung and bronchopneumonia.

It also occurs in scar tissue which has undergone hyaline change, as an encrustation on elastic tissue, in necrotic ganglion cells of the brain, in epidermoid carcinomas of the skin, in necrotic epithelial cells of the kidneys, in foci of pancreatic fat necrosis, in necrotic subcutaneous lipomas, in foci of caseous necrosis, in the intima of blood vessels, in arteriosclerosis, in uterine myomas, in adenomas of the thyroid, and in the walls of healing abscesses. A special type is calcification of the retained fetus—lithopedion. All available evidence indicates that dystrophic calcification depends upon local conditions, although it may be modified by general changes in calcium metabolism.

Calcinosis. Calcinosis is the term applied

tion may set in. Under these conditions if the nodules are not completely calcified, a chalky, thick fluid exudes through the ulcer. Microscopic examination of the typical nodule shows an irregular mass of calcium salts, surrounded by a zone of fibrosis and lymphocytic infiltration. There are numerous giant cells attached to the surface of the calcium deposits. The parathyroid glands are normal and there is no calcification in the internal organs (Rothstein and Welt).

Metastatic Calcification. In this type there is no preceding anatomic damage, and the deposits are chiefly in the kidneys, gastric mucosa, and lung (Fig. 32). It is observed especially in destructive lesions of bone. In the kidney calcium is deposited in the renal

tubules and in the surrounding stroma. In the gastric mucosa it is limited to the interglandular tissue about the open end of the glands of the fundus. Pulmonary involvement is an encrustation on the elastic fibrils and the collagen of the alveolar walls and the walls of the smaller capillaries, arteries, and veins. Similar lesions are produced in experimental animals by the ingestion of excessive amounts of vitamin D (Shohl, Goldblatt, and Brown).

spicules there is fibrous tissue or typical bone marrow.

Disturbances in the Metabolism of Phosphorus

Compounds of phosphorus are essential for fat and carbohydrate metabolism, and play an important role in the chemical reactions of muscular contraction and transfer of energy.



Fig. 33. Calcification of lung in tuberculosis. (Radiograph by courtesy of Dr. Sherwood Moore, M. I. R. 146643.)

Pathogenesis. It is evident that there are general and local causes for pathologic calcification, no one of which is operative in every example. The general causes are hypercalcemia and hyperphosphatemia, and the local causes are increased alkalinity of the tissues, local increase of phosphatase and inorganic phosphates, and preceding fatty degeneration or necrosis (Barr).

Ossification. Heterotopic Bone. In many older deposits of calcium there is gradual conversion to bone. It is assumed that the surrounding fibroblasts undergo metaplasia to osteoblasts, and the subsequent formation of trabecular bone. Between the trabeculae and

About 80 per cent of phosphorus in the body is in bone.

Requirements. In a balanced diet there should be one to one and one-half times as much phosphorus as calcium. In general, if calcium and protein are adequate, then phosphorus will be.

Effects of a Deficiency. Severe rickets develops in rats and dogs fed a low phosphorus diet (0.017 per cent), but no other change that is not attributable to inanition (Follis, Day, and McCollum). In all deficiencies there is mobilization of phosphate from the bones and consequent rarefaction and increased excretion of calcium. Phosphorus starvation in

farm animals occurs in those parts of the world where animals have been raised for centuries and the phosphorus reserves of the soil depleted.

Effects of an Excess. Increased dietary intake does not increase phosphorus in the body fluids, but a disturbance in the dietary ratio of calcium to phosphorus may result in defective deposition in bone (see the section on calcium). On the other hand retention of phosphorus because of chronic renal insufficiency may lead to pathologic changes.

Renal Retention of Phosphorus. Renal Rickets. Renal Dwarfism. In some instances of chronic renal disease there is retention of inorganic phosphate, so that the values in serum fluctuate from 5 to 12 mg. This results in two secondary changes: increased excretion of phosphorus by the intestine, carrying calcium with it and interfering with the normal absorption of calcium; and a state of chronic acidosis. Both of these result in hypocalcemia and mobilization of calcium from the bones. In children the demineralization of bones leads to defective and deficient growth, and in adults to the picture of osteitis fibrosa cystica (Albright, Drake, and Sulkowitch).

Disturbances in the Metabolism of Magnesium

The ash of normal bone contains 0.6 to 0.8 per cent of magnesium (Haury). The average for serum magnesium is 2 to 3 mg. per 100 cc., with 20 to 30 per cent in a nondiffusible form. Little is known concerning the requirement in man. It has been estimated that a child needs about 13 mg. per kilogram of body weight per day.

Effects of a Deficiency. In young rats and dogs fed a diet deficient in magnesium (2 parts per million), characteristic changes in the skin, kidneys, and teeth develop. There is dilatation of the cutaneous vessels, followed by extreme hyperirritability, with tonic and clonic convulsions—magnesium tetany. During the period of erythema there are focal necrosis and ulceration of the epidermis, with inflammation of the dermis. In the kidneys there is necrosis of the tubular epithelium with calcification. There are extreme hypertrophy of the gums, irregular deposition of dentine, degeneration of the odontoblasts, and formation of pulp stones. Chemical analyses of the tissues

show a decreased magnesium content of bone, but not of the soft tissues, and an increase of both calcium and phosphorus in the bones and the soft tissues.

Chronic Neurodermatitis. Engman and MacCardle have shown that the skin of patients with chronic neurodermatitis contains little or no magnesium. The relation of this to the cause of the disease is not clear, but it is the first demonstration of a mineral deficiency in a skin disease. The lesions are oval or polygonal, sharply defined aggregates of papules of gray-brown color. There are parakeratosis, hyperkeratosis, acanthosis, and hyperpigmentation of the epidermis, and slight infiltration of the dermis with polymorphonuclear leukocytes and monocytes.

Effects of an Excess. Large amounts of dietary magnesium interfere with the utilization of calcium, especially when there is an inadequate intake of phosphorus. The mechanism of the antagonism of calcium and magnesium is not yet clear.

Disturbances in the Metabolism of Iron

The body of the newborn infant contains about 0.375 gm. of iron, and that of an adult about 3 gm. This iron is in five basic forms: blood hemoglobin iron, 57 per cent; muscle hemoglobin iron, 7 per cent; parenchymatous iron, 16 per cent; available iron in other tissues, plus or minus 5 per cent. The iron of muscle hemoglobin and parenchymatous iron are not available for use in the regeneration of blood hemoglobin, even in the most extreme necessity.

Requirements. It is estimated that the average adult should eat not less than 12 mg. of iron a day to maintain a positive balance. Depending on many factors, it is improbable that more than 40 to 50 per cent of this is absorbed and utilized. Infants and adolescent children require more iron. In women the loss of 33 cc. of blood at each menstrual period, amounting to 0.298 gm. of iron per year, increases the requirement. Lactation requires 0.85 mg. per day. Pregnancy demands about 600 mg., including the requirements of the fetus and the loss of 350 cc. of blood at parturition. The manifestation of an iron deficiency (hypochromic) anemia is hence far more common in women than in men. The average American diet is so adequate in iron

that hypochromic anemia is seldom seen except when there is some additional causal factor (Hahn).

Formation of Hemoglobin. Hemoglobin is a combination of heme and a globin. Heme, in turn, is made up of protoporphyrin and iron. Hence to fabricate hemoglobin the body needs iron, pyrrole substances to form porphyrins and amino acids to synthesize the globin. Under normal conditions the iron is ingested with food or recovered from the physiologic destruction of hemoglobin. The amino acids are contained in the diet or are made available from the stored or the plasma proteins, and the pyrroles are synthesized. Following the loss of hemoglobin as after donation of 500 cc. of blood for a transfusion, the rate of regeneration in men is 0.49 gm. per 100 cc. of blood per day and in women is 0.040 gm. (Fowler and Barer). Ingestion of iron salts accelerates the velocity of regeneration.

The normal hemoglobin value for man is 15 gm. per 100 cc. of blood. As iron constitutes 0.336 per cent of the hemoglobin molecule, this means there is about 50 mg. of iron per 100 cc.

Destruction of Hemoglobin. After a life of about one hundred days the red blood cells are phagocytized by reticuloendothelial cells. Within the cell the hemoglobin is hydrolyzed and the iron is returned to the bone marrow or stored in the liver and spleen, and the porphyrin is converted into bilirubin and excreted by the liver (see chapter on diseases of the liver, p. 598 for a full discussion of this conversion).

Erythrophagocytosis. Under pathologic conditions, or following transfusions, there may be excessive destruction of red cells. In sections of the spleen, liver, lymph nodes, and bone marrow the mononuclear cells and the Kupffer cells are seen to be filled with red cells in all stages of disintegration—a process diagnosed as erythrophagocytosis.

Extravascular Destruction of Red Cells. If red blood cells leave the vascular channels, e.g., hemorrhage, they become foreign bodies and are phagocytized by mononuclear cells. From the hemoglobin two microscopically recognizable pigments are formed: hemosiderin and hematoidin, the former iron-containing and the latter iron-free and probably isomeric with bilirubin. Both are formed intra-

cellularly and the hematoidin or bilirubin is soluble and diffuses out of the cells. If it diffuses into the slightly alkaline living tissue it remains in solution and is not seen in sections, while if it diffuses into the slightly acid dead tissue it crystallizes (Rich).

HEMOSIDERIN AND HEMOSIDEROSIS. Hemosiderin is to be recognized microscopically as fine light brown granules, usually within the cytoplasm of large mononuclear cells. A light deposit is normally present in the liver and spleen, but under pathologic conditions, as in excessive destruction of blood, the deposit is greatly increased—a condition known as hemosiderosis. The involved organ is normal or slightly increased in size, rusty brown in color, and slightly increased in consistency.

HEMATOIDIN. Hematoidin is seen in infarcts and in other dead tissue as rhombic plates or as clusters of fine crystals arranged as a burr. It is never in large amounts and probably has no anatomic or physiologic significance.

The Fuscin Pigments. In the myocardial fibers and in the cytoplasm of ganglion cells and the epithelial cells of the seminal vesicles and prostate, yellow to brown granular pigment, increasing with age, is found. It is insoluble in fat solvents, is partially soluble in alkalis, does not give a reaction for iron, darkens with silver nitrate, stains lightly with fat stains and intensely with fuchsin. It appears to be identical with hemofuscin and to be formed in the disintegration of hemoglobin, probably as an intermediate product of hemosiderin (Connor). The excessive deposit of it in hemochromatosis will be discussed later.

BROWN ATROPHY OF THE HEART AND LIVER. In advanced age and in cachectic states the heart and liver may be small, firm, and dark brown. There is no conspicuous increase of connective tissue, but within the cytoplasm of the small parenchymal cells there is a light brown pigment. Careful studies will usually show a minimal associated deposit of hemosiderin.

Combinations of Hemoglobin. Normally hemoglobin forms a loose combination with oxygen and carbon dioxide, but under pathological conditions other gases may combine more firmly and may impair the ability of the blood to carry oxygen. The more important of these are sulfhemoglobin, the union of hemoglobin and hydrogen sulfide, formed in the intestine from excessive putrefaction, carbon

monoxide hemoglobin, and nitrous oxide hemoglobin, resulting from the inhalation of these gases. The tissue changes in all are those of anoxia; fatty degeneration of the liver and kidneys, hemorrhages in the serous membranes and viscera, and focal or central necrosis of the liver.

Methemoglobinemia. Methemoglobinemia may result from ingestion of toxic drugs or exist as a hereditary metabolic disorder (Graybiel, Lilienthal, and Riley).

Effects of a Deficiency of Iron. Anemia. For practical purposes a deficiency of iron is

there is a loss of a small amount of blood over a period of months or years. In addition to the loss of blood, most of these patients consume an inadequate diet, because of either anorexia or vomiting. In time the loss of iron through hemorrhage and the decreased consumption of iron lead to an anemia of the iron deficiency type. A similar condition is seen from time to time in women with menorrhagia, and in children with repeated profuse nosebleeds.

NUTRITIONAL. With a reasonably adequate intake of iron during pregnancy, the newborn

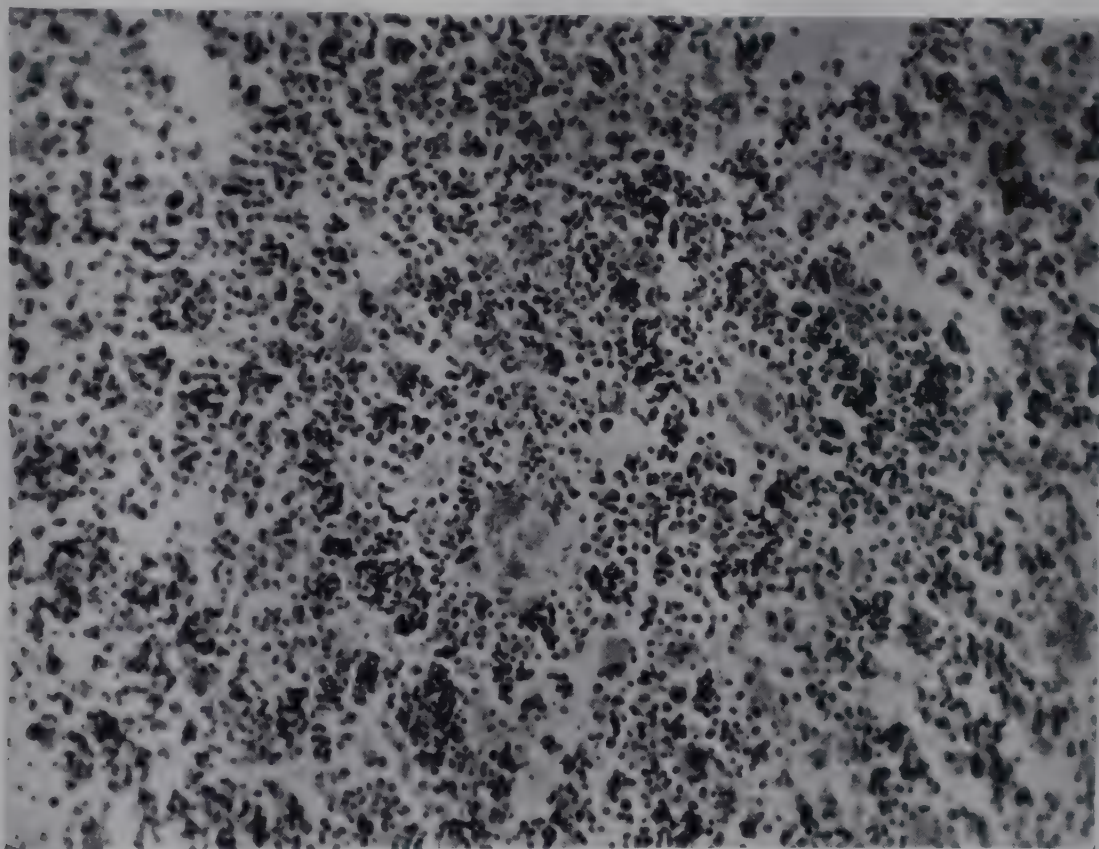


Fig. 34. Erythroblastic hyperplasia of the bone marrow.

synonymous with an iron deficiency anemia. Since it is only a symptomatic entity, there is no constant anatomic change in the tissues except in the bone marrow. Here there are hyperplasia of the red marrow and replacement of the fatty marrow by red marrow in direct proportion to the degree and duration of the anemia (Fig. 34). This hyperplasia is predominantly of erythroblasts and normoblasts. There is no storage of iron in the liver and spleen, in contrast with the situation in hyperchromic macrocytic anemia. If the anemia has been present for a sufficient length of time all the secondary changes of anemia will be present.

Types and Causes of Iron Deficiency Anemia. **LOSS OF BLOOD.** In ulcerative lesions of the gastro-intestinal tract, notably carcinoma of the stomach and colon and peptic ulcer,

infant is protected for the first four months of life. However, after four months the infant must be given a sufficient amount of iron, not only to meet the requirements of the weight at that time but also for rapid growth. The daily requirements vary from 5 to 15 mg. (Heath and Patek). The associated vitamin B deficiency has no influence on the efficacy of iron in the treatment of hypochromic anemia in pellagrins (Moore, Minnich, Vilter, and Spies).

CHLOROSIS. The disease chlorosis was well known in the medieval ages, but has become increasingly rare with modern civilization and greater attention to diet. It is a condition seen only in young girls from fifteen to twenty-five. The skin has a peculiar yellowish green color, and the skin and mucous membranes are pale. There is frequently menorrhagia, and a history

of inadequate diet for months or years. This inadequate intake plus the loss of blood at each menstrual cycle—about 33 cc.—if continued for several years will lead to a deficiency of iron and the appearance of hypochromic microcytic anemia. There is a prompt response to the administration of iron or of an adequate diet. Subclinical instances of chlorosis are probably common (Patek and Heath).

PREGNANCY. During pregnancy there is a gradual hydremia of blood and consequently a count of the number of red blood cells per cubic centimeter will reveal a decrease. In addition to this physiologic change there is also the not uncommon true iron deficiency

Hemochromatosis. Hemochromatosis is a disease characterized by excessive deposits of hemosiderin and hemofuscin in the liver, pancreas, and other organs.

Pathologic Anatomy. The liver is usually greatly enlarged and has a rusty red or ochre color. The parenchyma is broken up into nodules, isolated from one another by dense, firm, connective tissue. An iron-containing pigment, hemosiderin, is present in the hepatic cells, in the fibrocytes, extracellularly in the connective tissue, in the Kupffer cells, in the walls of the blood vessels, and in the epithelium of the bile ducts. A second pigment, iron-free hemofuscin, is found in the connective tissue of the



Fig. 35. Hemochromatosis of liver. (MacCullum: Textbook of Pathology.)

anemia during the latter months of pregnancy. It probably results from both an inadequate diet and a drain on the iron reserves of the mother for the late gestational storage of iron in the fetus, amounting to 15 mg. a day.

IDIOPATHIC. Despite the most searching investigation of patients with hypochromic microcytic anemia, about 5 per cent present a type of disease which responds to iron but in which none of the above factors can be elicited by either clinical or laboratory methods. It occurs predominantly in women in the third to the fifth decades of life, and in some instances is associated with the complete Plummer-Vinson syndrome. It is possible that there is defective secretion of gastric juice and faulty utilization or synthesis from the diet of minerals which are necessary for the formation of hemoglobin (Wintrobe and Beebe). (Full discussion, p. 643.)

adventitia of the vessels, in the smooth muscle cells of the media of arteries and veins, in the connective tissue cells, and occasionally in the hepatic cells. The pancreas is usually slightly larger than normal, firm, and deeply pigmented. There is a marked increase of both intralobular and interlobular connective tissue, and both hemosiderin and hemofuscin are easily identifiable. The islands of Langerhans are in part destroyed and replaced by pigmented connective tissue. The spleen is enlarged to twice normal size, is firm and deep purple in color. Both pigments can be seen microscopically, but are not in sufficient amount to change the color of the organ. Similar deposits of pigment are found in the epithelium of the kidney, in the glandular cells of the stomach and small intestine, in the myocardial fibers, in the mucosa of the respiratory tract, in the cortex of the adrenal gland, in the

epithelium of the genital tract, in the lymph nodes, and in the bone marrow. Aside from pigmentation of the choroid plexus the brain is characteristically not affected. In the skin there is a brown pigmentation, most marked on the exposed surfaces, in the folds, and about the external genitalia. The deeper color is the result of an increased amount of melanin and a deposit of hemosiderin.

Chemical Aspects. In most of the organs there is an increase in chemically recoverable iron: in the liver 1.5 gm. per 100 gm. of wet tissue as compared with the normal of 0.1 per cent. There is also an increase in copper: 27.6 mg. per kilogram of wet tissue, as compared to 5.97 for the normal liver.

Incidence. Hemochromatosis is a disease of men in a ratio of about 20 to 1, during the age period of from thirty to sixty. In an occasional example there is a familial or hereditary element.

Causal Factors. Many theories have been advanced for the cause of hemochromatosis: a destruction of blood; the action of toxins such as copper, bacteria, alcohol, zinc, and lead; and a disorder of metabolism of iron in the cytochrome system. The latter theory seems to fit best the known facts. An anatomically identical lesion in the tissues is observed in patients with aplastic anemia who have received numerous transfusions.

Clinicopathologic Correlation. In about 80 per cent of patients the changes in the pancreas are associated with diabetes mellitus, and the combination of this disturbance in carbohydrate metabolism with the characteristic pigmentation of the skin is the basis for the name "bronzed diabetes." The fibrosis in the liver obstructs the portal circulation, with all of the changes incident to this—ascites, dilation of the veins, and varices of the esophagus and about the rectum. The average duration of life after establishment of the diagnosis is eighteen months, and death results from the diabetes, from portal obstruction and rupture of esophageal varices, from cardiac failure, or from intercurrent infection.

Carcinoma of the Liver in Hemochromatosis. As in the ordinary type of cirrhosis of the liver, carcinoma in hemochromatosis is a frequent complication, occurring in at least 7 per cent of all reported cases. The subject is fully discussed in the section on carcinoma of the liver (p. 615) (Berk and Lieber).

Disturbances in the Metabolism of Copper

Copper is an essential part of all protoplasm, and the average daily intake should not be less than 2 mg. In lower animals it serves as the metallic part of the blood pigment, hemocyanin. In mammals it is an integral part of some enzyme systems, and is necessary for the transformation of iron into hemoglobin.

Effects of a Deficiency. Nutritional Anemia of Infancy. In many infants a mild degree of anemia develops, while in a few it is clinically manifest and requires medical attention. It has been observed that a severe anemia develops in rats fed a diet limited to milk from the time of weaning, and that the addition of small amounts of copper to the diet cures this anemia (Elvehjem). There is some question whether or not babies ever develop an anemia resulting from copper deficiency, since most human diets supply an adequate amount of this mineral. There is little doubt, however, that administration of copper with iron in certain anemias of infancy and childhood results in a more rapid response than can be secured with iron alone (Cason).

Disturbances in the Metabolism of Iodine

The body of an adult man contains about 50 mg. of iodine, one-half of which is in the muscles, one-fifth in the thyroid, one-tenth in the skin, and one-seventeenth in the bones.

Source and Requirements. About 200 micrograms of iodine are required daily for the maintenance of normal metabolism. There are increased demands in puberty, pregnancy, and lactation, during the course of infectious diseases, and by those ingesting a high calcium diet.

Turnover. Persons living in regions where goiter is not prevalent have an average daily urinary excretion of iodine of 165 micrograms, while those living in districts where goiter is prevalent excrete an average of only 42 micrograms. There is an increased excretion in hyperthyroidism, during menstruation and pregnancy, after surgical operations, and after the administration of iodine. Fasting decreases the urinary excretion. The blood level of iodine varies from 3 to 20 micrograms per 100 cc. It is higher during pregnancy and parturition and in hyperthyroidism. In hypothyroidism

the blood iodine in hormonal form is decreased, but the free form is not changed. There are rarely changes in diseases unrelated to the thyroid (Curtis and Fertman).

Effects of a Deficiency. Endemic Goiter. Endemic goiter is fundamentally a result of an iodine deficiency, but the exact mechanism has not yet been elucidated.

Pathologic Anatomy. The appearance of the thyroid gland in iodine deficiency is the result of the counteraction of two opposing factors: hypertrophy and hyperplasia with

Geographic Distribution. The highest incidence of endemic goiter is in peoples living in the Alps, Pyrenees, and Himalaya Mountains, in the Thames Valley in England, in the region of the Great Lakes and the Pacific Northwest of the United States, and in certain districts of New Zealand. In these regions there is restricted intake of iodine, either because of the low iodine value of the soil or the character of the food. In Japan the people are practically free of goiter, probably because of the ingestion of seaweed, rich in iodine.

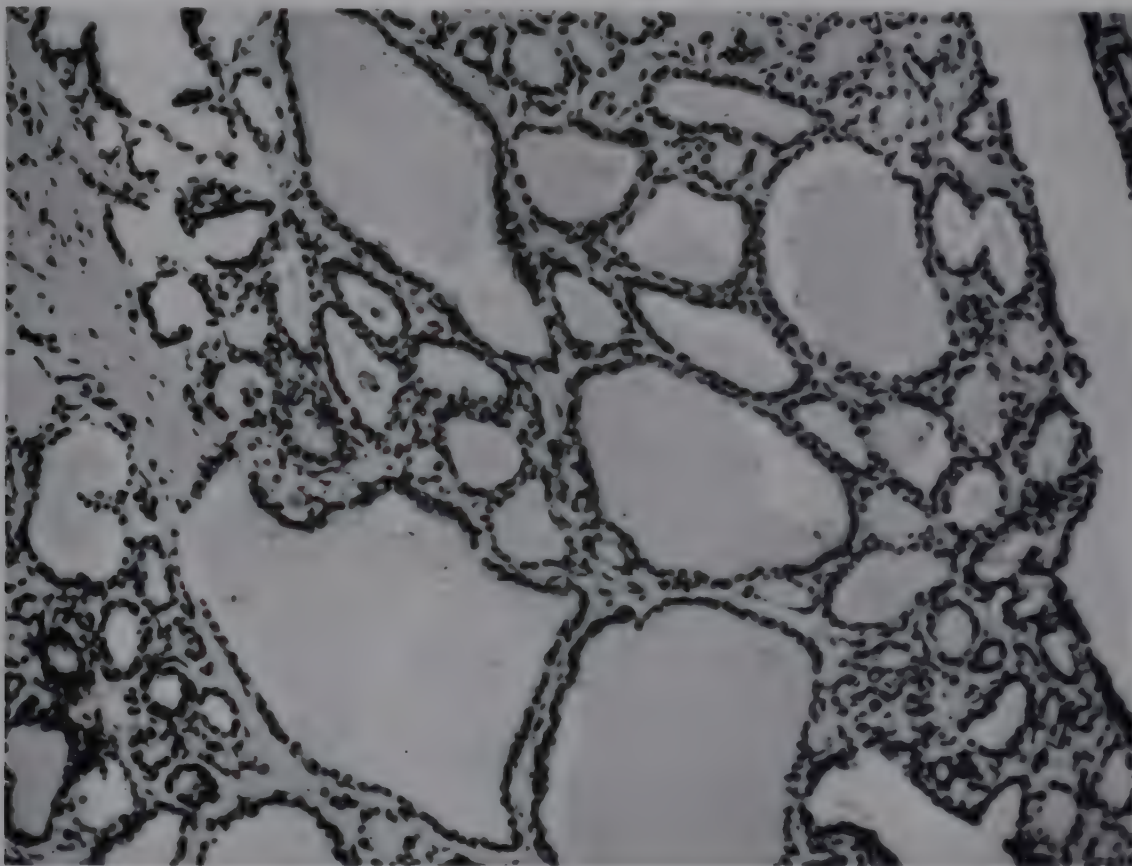


Fig. 36. Thyroid gland in endemic goiter.

release of colloid, and involution with storage of colloid. In turn these two factors depend on the supply of iodine and the demands for metabolism. If the available iodine is low or the demand is great, hypertrophy and hyperplasia result; while if iodine is adequate or the demands are minimal, involution results. With a preponderance of hypertrophy and hyperplasia the gland is normal in size or slightly enlarged, firm and gray. There is little visible colloid. The acini are small and numerous, and the epithelial cells are tall columnar in form. With a preponderance of involution and colloid storage, the gland is moderately increased in size, firm slightly lobulated, brown, and translucent. The acini are large, filled with colloid, and lined with low cuboidal or flat cells. All gradations between, and mixtures of the two basic changes, are encountered (Marine and Lenhart).

Prophylaxis. Marine and Kimball first demonstrated in the school children of Akron, Ohio, that the ingestion of small amounts of iodine would prevent endemic goiter. There has been ample confirmation of these observations and it may be accepted as good practice to add 0.2 per cent of potassium iodide to all common table salt.

Effects of an Excess of Iodine. In the therapeutic use of iodine and iodides the syndrome of iodism may appear, ranging from a mild coryza or a moderate acne, to a severe dermatitis with systemic reaction.

Disturbances in the Metabolism of Trace Elements

Manganese. Manganese is essential for reproduction, lactation, bone formation, and growth.

Effects of a Deficiency. In rats there is an increasing effect of manganese deficiency—first, ataxia in the offspring, then nonviability of fetus, and finally, disturbances of the estral cycle and sterility (Shils and McCollum).

Effects of an Excess. In experimental animals excessive ingestion or injection of manganese salts leads to cirrhosis of the liver and degenerative changes in the brain, particularly in the extrapyramidal system. By diet alone man cannot ingest toxic amounts of manganese, but in men working about powdered

corrosive poison—congestion, necrosis, and ulceration of the upper alimentary tract. Fungicides and fireproofing solutions containing zinc chloride may cause escharotic ulcers of the skin. In industry, “smelter chills,” “brass founders’ ague,” and “braziers’ disease” are probably the result of inhalation of fumes or ingestion of dust containing zinc (Hayhurst).

Cobalt. Cobalt has been demonstrated to be an indispensable dietary element for cattle and sheep. If it is essential for rats the effectiveness is most remarkable, since the entire body of

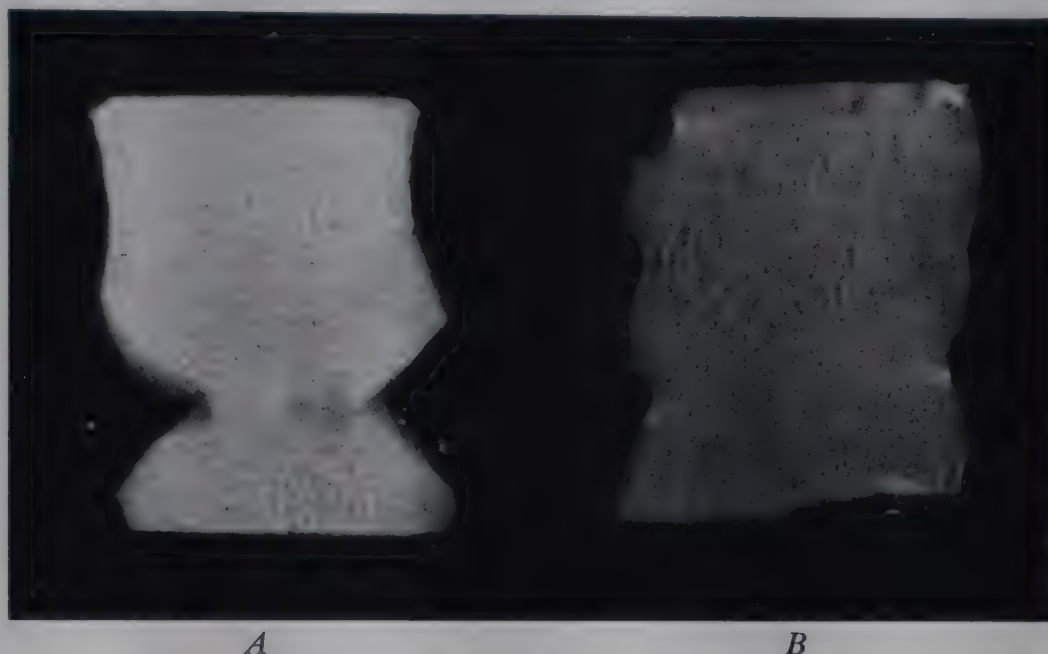


Fig. 37. *A*, Radiograph of bone of animal that had been fed fluorides. *B*, Normal bone. (Armed Forces Institute of Pathology, Neg. No. 74195.)

manganese ores, a definite clinical syndrome, not unlike that of progressive lenticular degeneration, is observed.

Zinc. Zinc is found in traces in all animal tissues and is most abundant in the liver and pancreas. It is associated physiologically with insulin, and apparently is an essential constituent of the enzymes carbonic anhydrase and uricase. Man requires about 0.3 mg. per kilogram body weight daily.

Effects of a Deficiency. It is unlikely that animals ever have a deficiency of zinc except under experimental conditions. Rats fed a diet containing one-half the needed zinc grow more slowly, have delayed intestinal absorption, and develop an abnormal fur coat (Hove, Elvehjem, and Hart).

Effects of an Excess. An excess of zinc may be ingested with acid-containing foods such as milk and vinegar, preserved in zinc vessels. These quantities fed to rats for four months do not affect the general health (Salant). Accidental or suicidal ingestion of zinc salts, sulfate or chloride, produces the changes of a

an older rat contains not over 0.01 mg. of cobalt (Stare and Elvehjem).

Effects of a Deficiency. In New Zealand, Australia, and along the Gulf and South Atlantic coasts of the United States there is a disease of sheep and cattle known as “bush sickness,” “pines” or “enzootic marasmus.” It is characterized by long, rough hair, hyperkeratosis of the epidermis, listlessness, anorexia, muscular atrophy, and retarded development of the secondary sexual organs. It is caused by a deficiency of cobalt in the food.

Effects of an Excess. Rats fed powdered cobalt or cobalt salts in amounts of 0.5 to 2 per cent of the diet develop a true polycythemia with an increase of blood volume (Orten, Underhill, Mugrage, and Lewis). Stare and Elvehjem found that the presence of as little as 0.04 to 0.05 mg. of cobalt in the entire body of a rat was sufficient to produce polycythemia. There are no satisfactory observations on the metabolism of cobalt in patients with polycythemia vera.

Fluorine. There is as yet no proof that fluor-

ine is an essential mineral, but definite effects of a deficiency and an excess are known in man.

Effects of a Deficiency. Most investigations, but not all, show that the addition of fluorine to drinking water up to 1 part per million, or the topical application of a fluoride to the teeth, reduces the incidence of dental caries (Knutson and Armstrong). No systemic effect has been demonstrated (McClure).

Effects of an Excess. An excess of dietary fluorine results in definite pathologic changes in man and in animals in the teeth and in the bones (Fig. 37). The teeth of man appear dead white and unglazed, have chalky white

Effects of an Excess. Selenium in the grain and other food fed to domestic animals causes a disease termed “alkali disease” in parts of the western United States. The pathologic changes are erosion of bones, loss of hair, anemia, deformed and tender feet, and loss of hoofs (Nutrition Reviews).

Boron. Although boron is essential for plants, and is present in animal tissues, no specific effects of a deficiency have been demonstrated.

Aluminum. Aluminum is present in plant and animal tissue but no observable effect of a dietary deficiency in animals has been elicited.

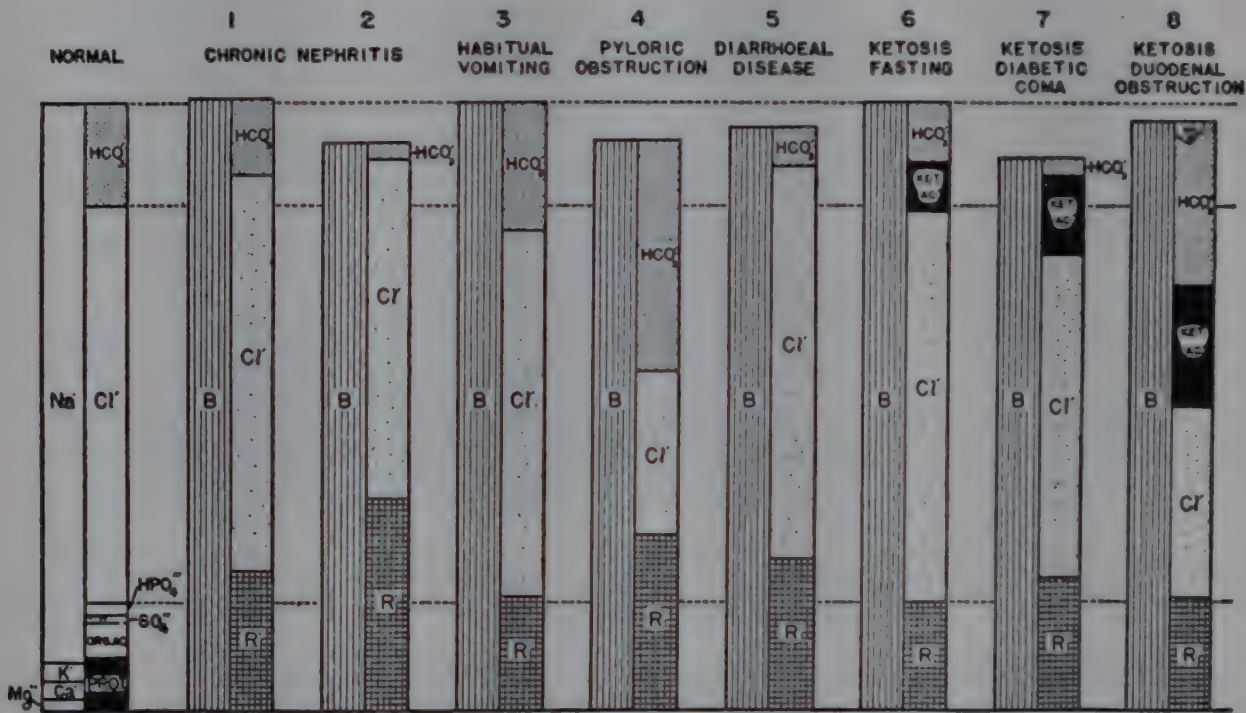


Fig. 38. Relation of alterations of electrolyte structure of plasma, produced by various conditions of disease, to change in bicarbonate. (After Gamble.)

patches in them, and become irregularly stained, hence the designation “mottled enamel.” The distribution is definitely correlated with the amount of fluorine in the drinking water, and amounts in excess of 1 part per million may induce it. The soft enamel appears to be more labile to decalcification and formation of the cavities of dental caries. In domestic animals fed rock phosphate which contains fluorine there are in addition osteopetrosis and enlargement of the bones of the skull, the ramí of the mandibles and of the long bones by deposit of new periosteal bone (Bauer). There is some evidence that excessive dietary fluoride leads to bony deformities in man (Kemp, Murray, and Wilson).

Selenium. Selenium is the only dietary element known to be absorbed from the soil by plants in quantities sufficient to produce poisoning in animals when the plants are eaten.

Acid-Base Balance: Acidosis. Alkalosis.

Normally there is a definite ratio between the basic (sodium, potassium, calcium, and magnesium) and the acidic (bicarbonate, chloride, phosphate, sulfate, organic acids, and protein) constituents of the body fluids. The changes in them in a few of the more important diseases and conditions are shown in Figure 38. The kidney is largely responsible for the control of the acid-base balance. It accomplishes this through excretion of a fluid more acid (up to pH 4.8) than blood plasma, thus making possible elimination of phosphoric acid and organic acids with an expenditure of only a little more than half the base which covers them in the blood plasma.

In evaluating the pathologic anatomy of acidosis and alkalosis it is difficult to separate cause and effect. There are no definite and

consistent changes in the tissues in these physiologic disturbances aside from epithelial degeneration and calcification in the renal tubules which have been described in patients receiving large amounts of alkali as a therapeutic agent in peptic ulcer (Kirsner, Palmer, and Humphreys).

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VII

Disturbances in the Metabolism of the Fluids of the Body

Water is the most abundant constituent of tissue. It is present as free and bound water, and as water of crystallization, and constitutes 65 to 75 per cent of the body weight, depending on species, degree of obesity, and other factors.

Intake of Water. In general a human being in north temperate climate requires 1 cc. of water for each calory of dietary intake. In practice, 50 per cent of this amount is consumed in the form of beverage, 38 per cent is ingested as preformed water of food, and 12 per cent is realized as water of oxidation within the body (Sunderman).

Output of Water. Water is lost from the body in urine, feces, expired air, sweat, and insensible perspiration. This loss proceeds at a certain minimal rate, independent of a lack of adequate amounts of water in the tissues. Thus for every square meter of body surface 680 cc. of water is lost every twenty-four hours, regardless of restricted intake, dehydration of the tissues, or concentration of the blood. This fact is important in evaluating the physiologic changes in persons stranded in the desert or in open lifeboats. In normal persons with a balance of intake and output at basal conditions the partition of the output is 30 per cent in the urine, 3 per cent in the feces, 12 per cent through the lungs and as insensible perspiration (about equally), and 55 per cent in the sweat. In exercise the increase in the sweat in cubic centimeters is $1.73 \times 0.55 \times$ the large calories of energy expended. The percentage partition is of course influenced by many factors. Increase of body or environmental temperature causes absolute and relative increase of loss in the sweat and insensible perspiration. Increase of the rate and depth of respiration and dryness of the air result in an increased loss through the lungs; while a high humidity of the in-

spired air may result in water being absorbed rather than lost through the respiratory tract. Diarrhea increases the loss in the feces. In all of these conditions there is an absolute and relative decrease of other pathways of output, but never below the minimum of about 400 cc. in the urine, 30 cc. in the feces, and 250 cc. by all other routes per square meter of body surface.

Turnover of Water. In addition to the fluids lost to the body by excretion, water in the form of secretion is poured into hollow viscera or into the intercellular spaces, and reabsorbed. In each twenty-four hours the minimal values are: salivary glands, 500 cc.; stomach, 1000 cc.; intestine, 700 cc.; pancreas, 700 cc.; liver, 100 cc.; and lymph, 700 cc.; a total of 3700 cc. (Adolph).

Fluid Partitions. Maintenance of Balance

There are many factors which control or influence the balance of water between an animal organism and the environment, and within the fluid compartments of the body.

Fluid Partitions. It is convenient in the evaluation of both normal and abnormal conditions to divide the body water into two major fractions and subdivide one of these into two parts (Sunderman):

1. Intracellular water—45 to 50 per cent body weight.
2. Extracellular water—25 per cent of body weight.
 - a. Intravascular fluid—5 per cent
 - b. Interstitial fluid—20 per cent

Total Fluid Volume. Injected water is equilibrated between the three fluid components within an hour. Hence, water containing heavy hydrogen—deuterium—may be used to de-

termine the total volume. Average figures are 70 to 75 per cent of body weight (Moore).

Extracellular Fluid Volume. Substances such as radioactive sodium, sodium thiocyanate, and urea which diffuse rapidly through fluids but enter cells slowly are used to determine the extracellular fluid volume. Average figures are 25 per cent of body weight, or 33 per cent of total water.

Intravascular Fluid Volume. Although all methods for determination of the blood volume have inherent errors, average figures are as follows: 4635 cc. total volume, or 72.4 cc. per kilogram of body weight, or 2750 cc. per square meter of body surface (Peters).

Maintenance of Balance Within the Body. Preservation of the relative ratios of fluid in the three compartments is dependent on the hydrostatic and osmotic forces within each partition, divided from one another by membranes which permit the free passage of water but not of solutes and colloids. Thus, a decrease of the plasma proteins lowers the osmotic force holding fluid (venous) in the intravascular compartment, while venous congestion increases the hydrostatic pressure in the intravascular compartment and limits resorption.

Although fluid is lost through lungs, skin, and intestine, the organ chiefly responsible for maintenance of the volume and composition of the body fluids is the kidney. In mammals, this is accomplished by the capacity of the kidney to excrete a urine with a higher osmotic pressure than the plasma from which it is formed.

Effects of a Decrease in the Total Fluids of the Body—Dehydration

Dehydration may result from a primary loss of water or a primary loss of salt (Sunderman).

Dehydration from Loss of Water. This type of dehydration is seen when there is excessive loss through the skin, as in fever or high environmental temperature, or through the kidneys, as in diabetes insipidus, or when there is decreased intake as in shipwrecked sailors or in those lost in a desert. Under these conditions the concentration of salt in the body fluids increases and there is a shift of fluid from intracellular to extracellular. The resulting severe intracellular dehydration probably

plays a role in producing death (Winkler, Elkinton, Hopper, and Hoff). This shift of fluid is probably caused by a loss of intracellular potassium in dehydration from water deprivation (Elkinton and Winkler).

Dehydration from Loss of Salt. Primary loss of salt is observed in adrenal insufficiency and in diabetic ketosis (Sunderman) and in patients with diarrhea or vomiting (Hartman). In all of these conditions there is loss of base



Fig. 39. A dehydrated, emaciated infant with diarrhea. (Photograph by courtesy of Dr. Alexis Hartman.)

and a consequent withdrawal of base and water from the intracellular compartment to preserve isotonicity of the extracellular fluids. The end result is intracellular dehydration.

At times a secondary type of dehydration from loss of salt may be observed in patients on the verge of salt depletion. The ingestion of large amounts of water and excretion of it with some salt will throw these patients into dehydration. Similarly the injection of hypertonic solutions may lead to excessive loss of water and dehydration.

Pathologic Anatomy. The pathologic changes of dehydration are limited to an excessive dryness of the tissues. The fat of the

subcutaneous tissue is dry and relatively opaque. In the serous cavities the organs stick to the gloved hand and the covering membrane does not have the usual shiny appearance.

Effects of a Decrease of Intravascular Fluid—Hemorrhage

It is extremely difficult to determine the exact effect or effects of the sudden loss of large quantities of blood. The only pathologic finding solely attributable to an exsanguinating hemorrhage is paleness of all the organs. From a physiologic standpoint there are a number of interesting alterations and adaptations.

After the sudden loss of from 500 to 1200 cc. of blood there are a decrease of right atrial pressure, decrease of arterial blood pressure, and slight tachycardia, especially on assuming the erect position (Shenkin, Cheney, Govons, Hardy, Fletcher, and Starr). If the volume output in liters per square meter of body surface falls below 2.6 there are symptoms of shock (Brannon, Stead, Warren, and Merrill). The total volume of blood and plasma is of course materially decreased, and in general it takes the animal organism from three to forty-eight hours to restore the volume of circulating fluid to normal. This restoration is accomplished by the withdrawal of fluid from the tissues. With the dilution of blood by fluid there is of course a corresponding fall in the number of red blood cells and in the values for hemoglobin. The percentage of plasma proteins is not materially changed during the period of dilution, and from this fact one may conclude that the body contains a store of readily available plasma protein, and that as the blood is diluted by fluid this protein enters the circulation and maintains normal values. Similarly there are only minor variations in the crystalloids of the blood, such as chlorides and urea. The regeneration of the red cells and of hemoglobin requires from three to seven days following a hemorrhage of about 1000 cc. in man. In more severe degrees of hemorrhage the store of plasma proteins is not sufficient, and the values for them fall after the second or third day and are only restored to normal after from seven to ten days (Wallace and Sharpey-Schafer; Whipple).

The effect of long-continued loss of blood

is much more closely related to the loss of iron than to the decrease of fluids, and the entire problem of the regeneration of hemoglobin is discussed in Chapter VI.

Effects of an Increase of Intravascular Fluid—Plethora

An increase in the volume of blood—"plethora"—may affect the entire body or only part, and may affect both cells and fluid or only fluid. Primary plethora, an increase of both cells and fluid, is seen in polycythemia, and is an essential part of the disease. Secondary or hydremic plethora is usually a temporary condition. The homeostatic mechanisms are such that a sudden increase in the total amount of intravascular fluid is rapidly adjusted by the excretion or transfer to the interstitial component of the body fluids. However, there may be serious consequences, or even death, before the adjustment can be made; or diseased organs may be inadequate to cope with the situation.

Hydremic Plethora. Water Intoxication. From the preceding discussion it is evident that any disturbance leading to decreased excretion of water may be associated with hydremic plethora, if the intake is not proportionally decreased. In practice this is seen in patients with renal insufficiency. If a person with chronic nephritis is given 10 liters of water daily, headache, dizziness, chills, vomiting, and dyspnea develop within a few days. If dogs are given pituitary extract to prevent diuresis and large amounts of water a similar train of symptoms follows and terminates in convulsions and death. The convulsions and many of the other symptoms are relieved by the ingestion of salt, so that it appears that water intoxication is caused as much or more by a dilution of the salts of the body fluids as by the excess of fluid (Greene and Rowntree). The pathologic changes of water intoxication are inconstant and inconspicuous.

In the therapeutic use of parenteral fluids it is important not to administer them so rapidly that hydremic plethora results. In normal men injection of up to 2000 cc. at a rate of 50 to 150 cc. a minute produces an increase of venous pressure, an increase in the diastolic size of the heart, and a diminution in vital capacity. If the heart muscle is the seat of disease and the volume of blood is suddenly

increased, cardiac failure with extreme edema of the lungs may result (Sharpey-Schafer and Wallace).

Localized Plethora. If the abdomen has been greatly distended by a tumor, by ascites, or by a pregnancy, and the cause of the distention is suddenly removed, the great veins may dilate and withhold large amounts of blood from the circulation. If, in addition, there is latent or evident cardiac disease, death from cardiac failure may occur within a few minutes.

Effects of an Increase of Extravascular Fluid—Edema

The capillary endothelium forms a semipermeable membrane separating the intravascular fluid from the interstitial fluid. In an adult man the total available capillary surface amounts to about 6300 square meters. If there were no physical or chemical forces to hold the fluid in the vessels, and if the capillary pressure were 10 mm. of mercury, the total plasma volume would be filtered into the interstitial space within ten seconds.

Chemical analyses of the concentration of electrolytes in the plasma and in interstitial fluid show that the capillary endothelium is freely permeable to them in accordance with the Gibbs-Donnan equilibrium. On the other hand, only 5 per cent of the plasma protein escapes into the interstitial fluid. It follows that there are two physical forces acting on each side of the capillary endothelium: the pressure of the fluid inside the capillaries tending to drive it into the interstitial spaces, and that in the tissues preventing transudation; and the colloidal osmotic pressure inside the capillary holding the fluid within the vessels, and that outside pulling fluid through the wall.

Factors Influencing the Movement of Fluids. In general terms, factors that will increase the movement of fluid into the tissues are: increase of capillary pressure, decrease of tissue pressure, decrease of colloidal osmotic pressure of the plasma, and increase of the colloidal osmotic pressure of the tissue fluids. The converse of each of these factors decreases the movement of fluids into the tissues or increases the movement of fluid into the vascular channels.

Normally there is a gradient of pressure in the vascular system, as shown in Figure 40.

In man arterial capillary pressure on the average amounts to 45 cm. of water, and the venous capillary pressure to 22 cm. of water. The colloidal osmotic pressure of the blood is about 36 cm. of water. Assuming that these are the only factors controlling the movement of fluid, it follows that at points in the vascular system with capillary pressure above 36 cm. of water, fluid will move out of the vessels, and at points with a pressure below 36 cm., fluid will move into the vessels.

Pathologic Alterations in Effective Filtration Pressure. Active and Passive Congestion. Under normal conditions the inflow and outflow of blood from any given part are delicately balanced, but in pathologic conditions the inflow may exceed the outflow and there is a shift of the pressure gradient to the venous side.

If the cause of the excessive inflow is arteriolar dilation the lesion is designated as "active congestion," while if the cause is obstruction to outflow the term "passive congestion" is applied.

When the shift is of slight degree or of short duration there are few changes other than an increase in the color of the part, such as in the acute active congestion of the face in blushing, or the acute passive congestion of the arm or leg when a constricting band is placed on it.

However, if the shift of pressure gradient to the venous side persists there is movement of fluid from the intravascular to the interstitial compartment and chronic congestion with edema. The condition may occur in a local part when there is partial occlusion of the venous return by a thrombus or external pressure, or in the entire body when there is cardiac or circulatory failure (see discussion p. 759).

The pathologic changes of chronic congestion are not only those of the passage of fluid into the interstitial component, but also those of increased vascular pressure with atrophy of surrounding cells, and those of deficient oxygenation with necrosis of the sensitive parenchymal cells and proliferation of the less sensitive fibroblasts.

Pathologic Alterations in Capillary Permeability. Capillary endothelium is a semipermeable membrane, allowing free diffusion of electrolytes, but holding 95 per cent of the protein in the plasma. Damage to the endothelium

resulting in increased permeability allows protein to pass into the tissues, lowers the colloidal osmotic pressure of the plasma, and increases the differential between capillary pressure and colloidal osmotic pressure. The result is edema.

Pathologic Anatomy of Edema (Exclusive of the Edema of Inflammation). Edematous organs or tissues are increased in volume and in weight. The covering structures, such as skin, serous membrane, and capsule, are stretched, smooth, and glistening. The tissue

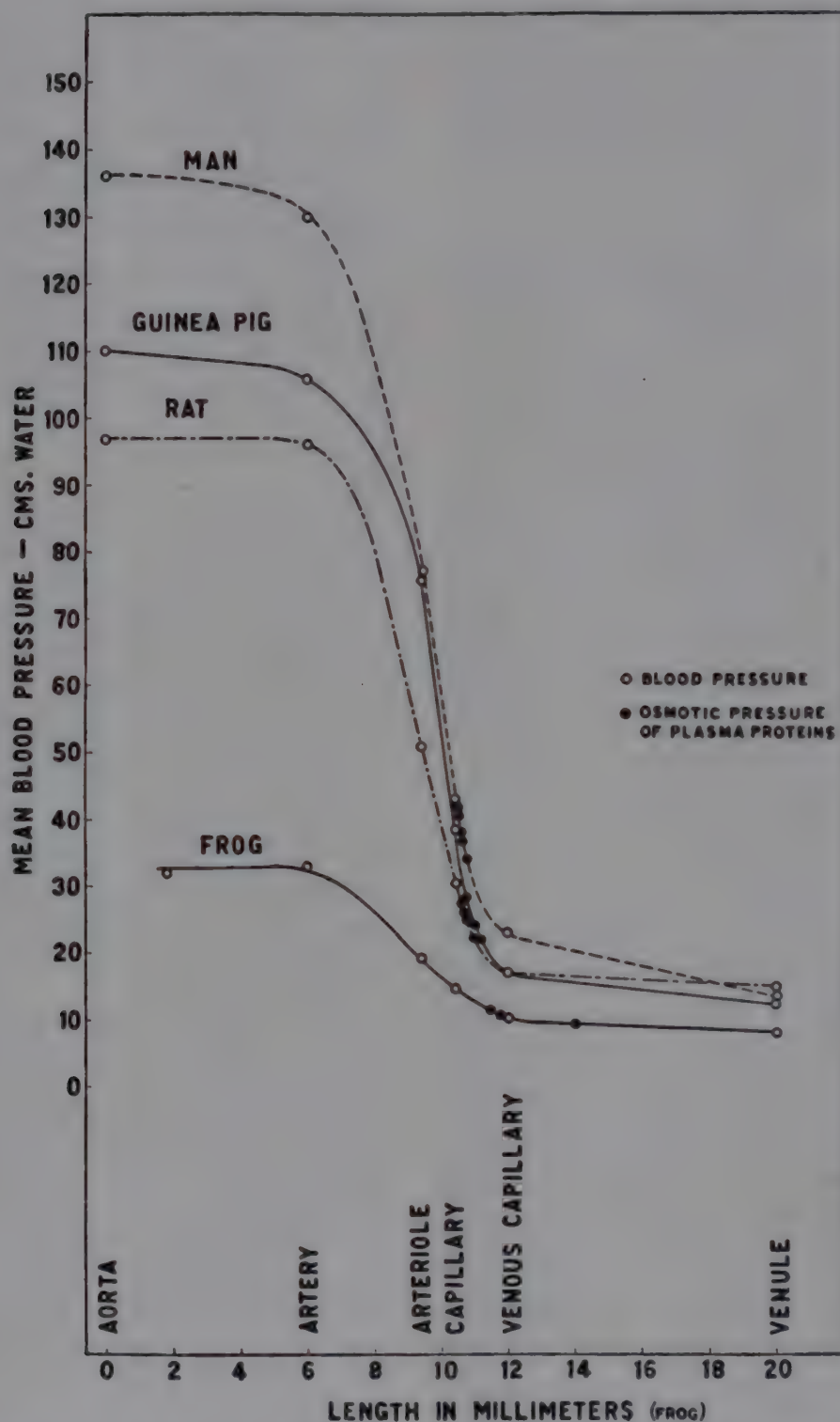


Fig. 40. Relation between capillary pressure and the osmotic pressure of the plasma proteins in four species. (After Landis.)

Pathologic Alteration in the Colloidal Osmotic Pressure of the Plasma. Whenever the total plasma protein falls below 4 gm. per 100 cc., or the plasma albumin below 1.5 gm. per 100 cc., fluid may pass into the tissues under force from the greater differential between capillary pressure and colloidal osmotic pressure. This is seen in the hypoproteinemia of starvation, advanced damage to the liver, and lipid nephrosis.

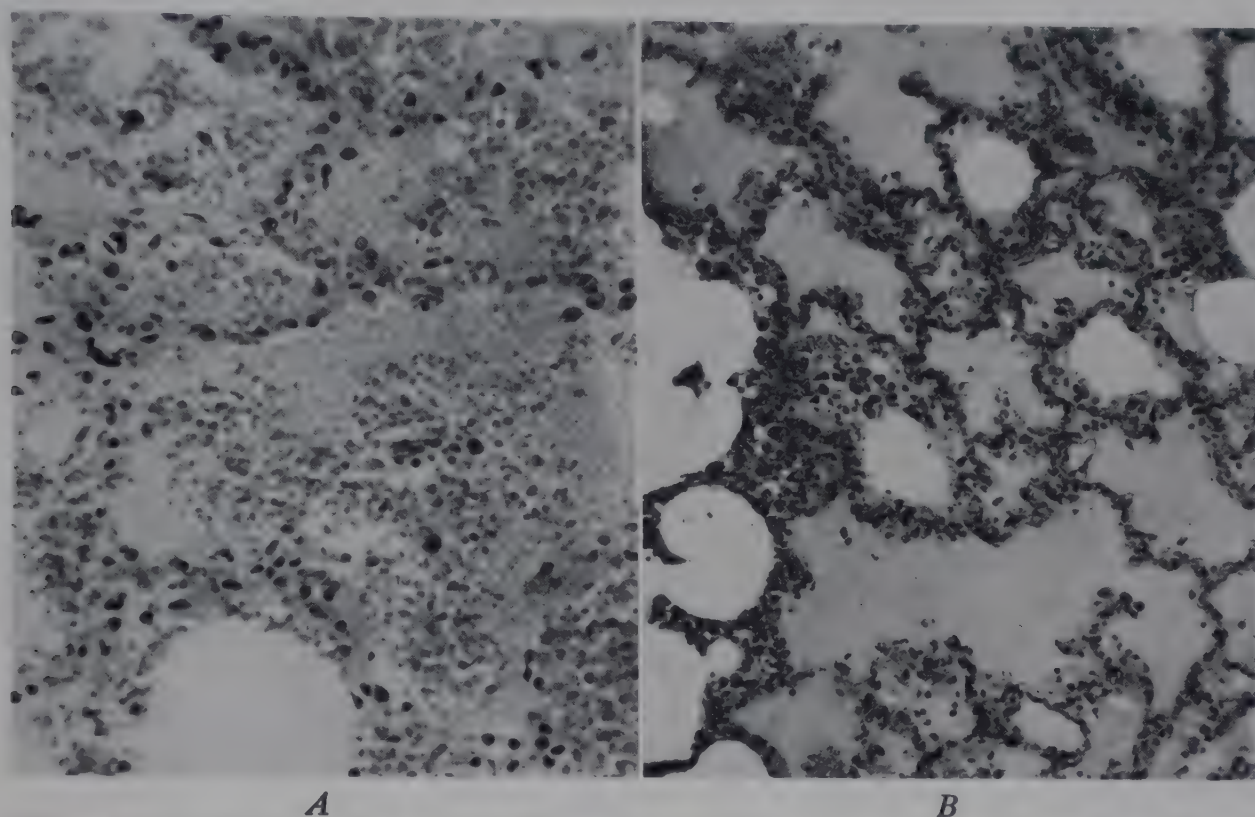
has a bluish gray translucent appearance, and when cut, a clear limpid fluid flows or can be expressed from the surface. In the lungs it is admixed with air and is frothy. If there is associated hemorrhage, the fluid is light pink in color. In organs with a characteristic architecture, the markings may be partially obliterated. Fluid that accumulates in the pericardial, pleural, and peritoneal cavities and in the tunica vaginalis is clear, limpid, and

light yellow, has a specific gravity less than 1.010, and contains few cells and little protein. There are two criteria for the recognition of edema in microscopic sections: separation of the tissue elements and presence of precipitated protein (rendered insoluble by the fixative employed). In edema of parenchymatous organs such as the liver the endothelium is lifted from the basement membrane and a finely granular acidophilic debris fills the intervening spaces (Fig. 55, p. 96). If there is an increase of cellular water, the cells

volume due to increased capillary permeability.

Types. From the preceding definition it is apparent that a wide variety of agents and events may cause shock. Hence it is difficult to classify them. However, from the extensive investigations during World War II, a fairly definite concept of three basic types of shock has emerged. These are primary, secondary, and hemorrhagic.

Primary or neurogenic shock is a neurovascular reaction similar to syncope or faint-



A

B

Fig. 41. Edema of the lung. *A*, With hemorrhage in a patient who died of shock. *B*, In a patient who died of cardiac failure.

are increased in size, and the cytoplasm is less dense or is vacuolated. In the lungs the fluid accumulates in the alveolar spaces. Microscopically it is seen as an acidophilic, acellular material, varying in density directly with the amount of contained protein. In the supporting tissue the collagenous and elastic fibrils are separated, and the spaces partly or completely filled with precipitated protein. Since most types of noninflammatory edema are associated with an increase of vascular pressure, dilatation of the capillaries is also observable in all of the types of changes described (Landis).

Disturbances in the Ratio of Intravascular and Extravascular Fluids—Shock

Shock is a clinical condition characterized by progressive reduction in circulating blood

ing. It may be initiated by pain, by nerve impulses originating in injured tissue, or by emotional disturbances. *Secondary* shock is that form which results from the action of "toxic substances" absorbed from injured areas, from foci of bacterial injections, or from dead tissue. *Hemorrhagic* shock is the type resulting from acute loss of blood.

In many patients all types are combined, as in a patient with a lacerated and contused wound. Initially there is primary and hemorrhagic shock followed by secondary shock.

Pathologic Anatomy. The pathologic changes are those of injury to endothelium and anoxia. There are congestion of vessels and petechiae in all tissues. In the lung there is edema. The parenchymal cells of the liver, kidney, adrenal, and heart show degenerative changes of cloudy swelling and necrosis. The soft tissues of the extremities are edematous

and there are effusions into the serous cavities. If death is delayed there is a hemorrhagic, edematous bronchopneumonia in the lungs (Moon).

Chemical and Physiologic Aspects. Shock is accompanied by a reduced total and effective blood volume; a reduced minute volume output of the heart and volume flow of arterial blood; hemoconcentration; an increase of the nonprotein nitrogen, glucose, and potassium in the blood; a reduction in metabolism, alkaline reserve, chloride, and oxygen content; delayed coagulability of the blood; and an increased flow of lymph in the thoracic ducts. (Gregerson).

Pathogenesis. All evidence points to capillary injury and increased capillary and cellular permeability as the basic disturbance in shock. There is some evidence that early in shock a vaso-excitor substance is liberated from the kidney, while late there is a vasodepressor substance formed in the liver and muscles (Shorr, Zweifach, and Furchgott).

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VIII

Disturbances in the Fluidity of the Blood

The proper functioning of the blood depends upon the maintenance of normal fluidity and on the integrity of the closed vascular system. Under normal conditions a small or even a large defect in the wall of a blood vessel is repaired by vasoconstriction and by clotting of the extravasated fluid. On the other hand the ability of the blood to clot must be so delicately balanced that there is no change from fibrinogen to fibrin within the vascular channels—i.e., thrombosis. If blood leaves a vessel through a visible defect it is known as “hemorrhage by rhexis,” while if the red cells permeate through the capillary walls it is known as “hemorrhage by diapedesis” or “parenchymatous hemorrhage.”

Classification of the Causes of Hemorrhage

The most satisfactory classification of the causes of hemorrhage is one based on an evaluation of two clinical tests: bleeding time and coagulation time. The normal values for these two determinations vary with the method used.

- I. Bleeding and coagulation times normal.
 1. Hemorrhage by rhexis from trauma or erosion of vessels.
 2. Damage of capillary walls caused by dietary deficiencies—scurvy.*
 3. Congenitally defective capillary walls—hereditary telangiectasis.
- II. Bleeding time prolonged and coagulation time normal.
 1. Hereditary pseudohemophilia.
 2. Purpura.
- III. Coagulation time delayed and bleeding time normal.
 1. Hypoprothrobinaemia resulting from a deficiency of vitamin K.*
 2. Hemophilia.

* Discussed in the chapter on dietary deficiencies, p. 539.

3. Fibrinogenopenia.

4. Excessive amounts of anticoagulants in the blood—anaphylactic shock.†

The Hemorrhagic Diseases

Hemorrhage by Rhexis. Interruption of the continuity of the vascular system may be brought about by physical trauma or by erosion of the wall by a disease process. The immediate reaction to complete section of a vessel is retraction of the cut ends into the tissue and vasoconstriction of both proximal and distal segments for a distance of several centimeters. This mechanism is probably more important in stopping hemorrhage than clotting of the blood.

Hereditary Telangiectasis. In this condition minute spider telangiectases, inherited as a simple mendelian dominant, appear particularly in the mucous membranes of the nose and mouth and skin of the face and neck during the third and fourth decades of life. Hemorrhage from them, especially after trauma, may be excessive, and may lead to a hypochromic anemia. In microscopic sections large sinusoidal spaces just beneath the epidermis are prominent.

Pseudohemophilia. In contrast with hemophilia, the only detectable abnormality in pseudohemophilia is a prolonged bleeding time. The condition is inherited as a dominant sex-linked character and occurs in children of both sexes (Estren, Medál, and Dameshek).

PURPURA

Purpura is a symptom, and signifies small or large hemorrhages into the tissue, originating without adequate physical trauma. Several varieties are recognized:

† Discussed in the chapter on hypersensitive states, p. 504.

- I. With thrombocytopenia:
 1. Primary.
 2. Secondary to infections, blood dyscrasias, and allergic states.
- II. With a normal platelet count:
 1. Simple, as in the aged.
 2. Schönlein-Henoch types.
 3. Nutritional, as in scurvy.

Primary Thrombocytopenic Purpura. By definition this is a purpura with a decreased number of circulating platelets and without demonstrable cause. It is sometimes known as "Werlhof's disease."

forty-five. The symptoms are related to hemorrhage into the tissues and a tendency to bruise from slight trauma. Bleeding into the brain, into the eye, and from the uterus may be a serious manifestation. Epistaxis is frequently troublesome.

Secondary Thrombocytopenic Purpura. In leukemia and aplastic anemia the thrombocytopenia is directly related to depression of the normal activity of the bone marrow, while in the infectious diseases there is evidence for both abnormal destruction and de-



Fig. 42. Hemorrhage into the gums of a patient with monocytic leukemia. There was an advanced thrombocytopenia. On the chin are the characteristic dermal lesions of monocytic leukemia. (Photograph by Dr. Malcolm Cook from files of Dr. Carl V. Moore.)

Pathologic Anatomy. The spleen is slightly enlarged and weighs 200 to 400 gm. In most instances the follicles are conspicuous, with hyperplasia of the reticulum cells in the center. In the pulp there are polymorphonuclear leukocytes, eosinophils, and megakaryocytes. There is no fibrosis. The bone marrow is essentially normal. Three theories, none entirely satisfactory, have been proposed to explain the deficiency of platelets: increased destruction by the spleen, elaboration by the spleen of a platelet-depressing factor, and a basic defect in the formation of platelets in the bone marrow.

Thrombocytopenic purpura has a sexual preponderance of 2 to 1 in women, and is most common between the ages of twelve and

pressed formation. Many drugs, notably benzol, allylisopropylacetylcarbamide, arspenamine, and the sulfonamides, are at times the cause of thrombocytopenia.

HEMOPHILIA

Hemophilia is a hereditary tendency to bleeding. The manifestations are seen in men, while women carry it as a recessive character. Pathologic changes are only those of hemorrhage. Hemorrhages are more commonly observed from the mucous membrane of the nose and mouth, into the alimentary and urinary tracts, and into the joints. Organization of the hemorrhage may lead to fibrosis, especially of the synovial membranes, with resulting ankylosis (Key). The bone marrow

may show hyperplasia. There is no decrease in the number of megakaryocytes in the marrow.

Defect in Clotting. The bulk of evidence points to a deficiency of thromboplastin, probably related to an abnormal stability of the blood platelets. The prothrombin, calcium, and fibrinogen in the blood of hemophiliacs are normal in amount.

Clinicopathologic Correlation. The signs of the disease—excessive hemorrhage from trivial cuts and bruises—usually appear during the first or second year of life. The hematomas

Thrombi and Thrombosis

A thrombus is a solid mass formed within a vessel from preexistent constituents of the blood or lymph during life. An *agglutinative thrombus* is composed only of the cellular elements, while in a *fibrin thrombus*, fibrin forms the basic structure. Because of the frequency and importance of fibrin thrombi, most pathologists use the word “thrombus” without qualification for this type, and a modifying adjective for all other types. “Thrombosis” is the formation or development of a thrombus.

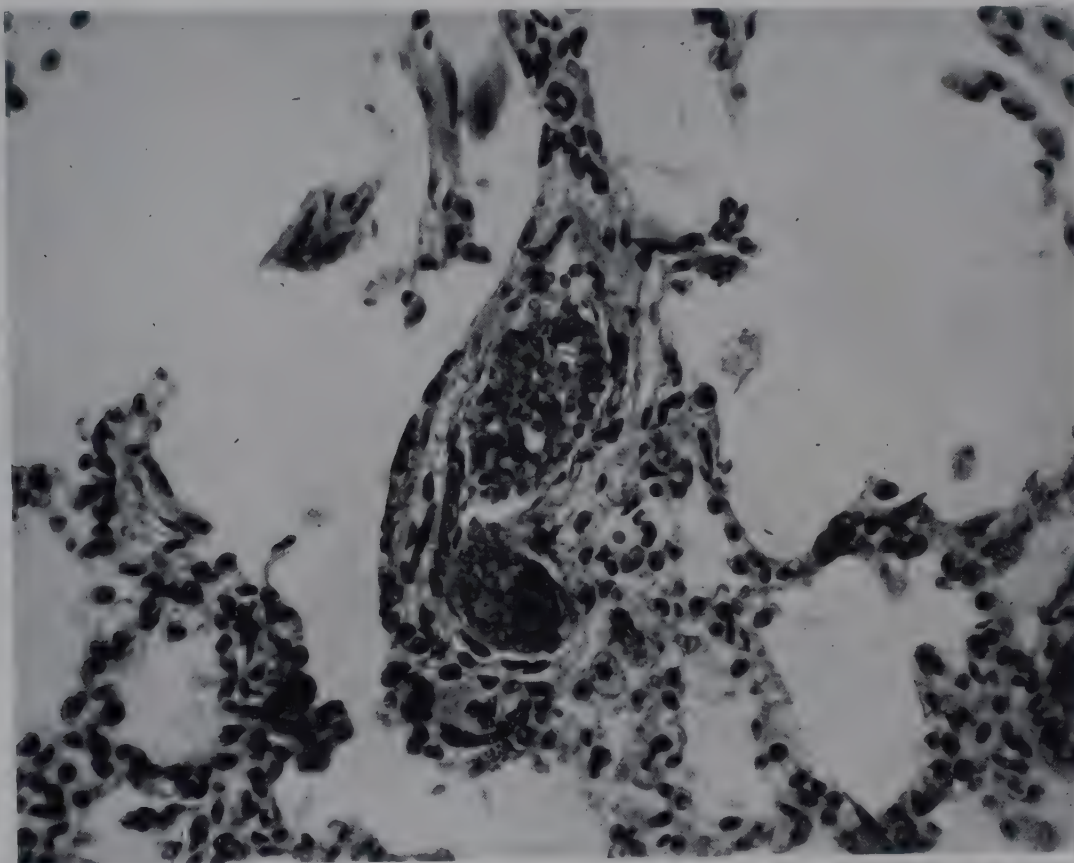


Fig. 43. Agglutinative thrombi of red cells in the pulmonary vessels. From a child who received a transfusion ten hours before death.

may press on nerves and cause neuralgia, or on blood vessels and result in gangrene. Bleeding from the kidneys with the passage of clots through the ureters causes excruciating pain. Death from exsanguination occurs in most patients before the tenth year. The extraction of a tooth in one of these persons is particularly serious, and the bleeding into the joints is one of the outstanding clinical manifestations.

FIBRINOGENOPENIA

This rare congenital, possibly hereditary, condition is characterized by a complete absence or a decreased amount of fibrinogen in the blood. The pathologic changes are not well defined and the cause is unknown. Death results from exsanguination (Schönholzer).

Agglutinative Thrombi. Of the three cellular elements of mammalian blood, platelets, red cells, and white cells, agglutinative thrombi composed of the first and second are known. The existence of an agglutinative thrombus made up of white cells has not been established.

Platelet Thrombi. These thrombi are found particularly in the small pulmonary capillaries and venules, in the small venous sinusoids of the spleen, and in the capillaries of the brain. In microscopic sections they appear as homogeneous hyaline masses, adherent to the wall, or completely occluding the vessel. Decreased rate of blood flow, increased viscosity of the blood, and injury to the endothelium are the more important contributing factors.

Red Cell Thrombi. Agglutinative thrombi

composed of red blood cells are also seen in the capillary vessels, early as clumped cells and later as hyaline masses. The most important cause in man is transfusion of mismatched blood.

Mechanism of Agglutination. Three theories, none proven, have been proposed to explain the agglutination of the cellular elements of the blood: (1) an alteration in the ectoplasmic layer of the cells which makes them sticky, (2) a loss of the electrical charge on the cells, so that they no longer repel one another, and (3) adsorption of a protein on

elastic postmortem clot; it overdistends the vessel; it possesses a definite structure with lines of Zahn; and it is adherent to the wall.

Formation of Thrombi. In experimental animals it is possible to follow serially the histologic changes in thrombosis. If the wall of a large vein is injured, within a few hours platelets are deposited over the injured area in perpendicular trabeculae, leaning with the flow of the blood. Soon thereafter white blood cells in large numbers accumulate on the surface of the conglomerated platelets, and finally the blood between the trabeculae clots and

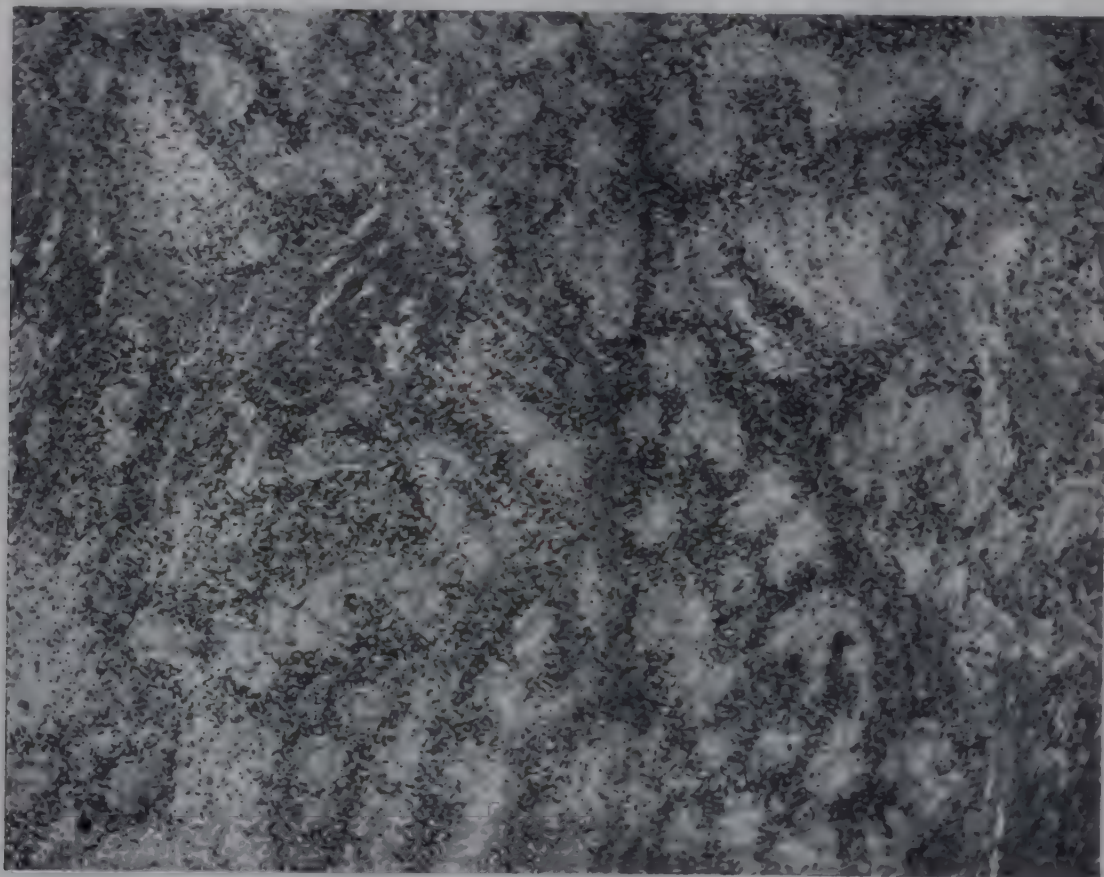


Fig. 44. Recent thrombus showing the lamina of platelets and margination of white cells.

the surface of the cells which makes them sticky (Silberberg).

Fibrin Thrombi. The formation of a fibrin thrombus is essentially the clotting of blood.

Structure of Thrombi. The typical thrombus is mottled reddish gray, and over the surface has riblike markings of interlacing white or gray trabeculae, known as the lines of Zahn. These trabeculae are clearly visible on the cut section, and represent hyaline masses of conglomerated blood platelets. Between these coral-like trabeculae there is a fibrillar, dark red, friable mass of fibrin, red cells, and white cells. A thrombus is to be distinguished from a postmortem clot on the basis of the following characteristics: it is mottled rather than a uniform dark red; it is firm, dry, and friable in contrast with the

traps within it a number of red blood cells. On the basis of these histologic changes it is reasonable to conclude that the disintegration of the platelets liberates a thromboplastic substance, which in turn causes the fibrinogen to be converted into fibrin.

Varieties and Types of Thrombi. Thrombi are described as *red* or *white* on the basis of color; as *primary* or *secondary* on the basis of whether they are formed from circulating blood or from stagnant blood; and as *mural* or *occluding* to designate whether the thrombus projects from the wall into the blood or completely fills the lumen. Other qualifications such as *marantic*, *ball*, *autochthonous*, *infected*, and *stratified* are applied to thrombi.

Secondary Changes in and Organization of Thrombi. Within a few days after a thrombus

forms there are proliferation of fibroblasts, invasion by endothelial sprouts and capillaries, and beginning organization. The fibrin and dead tissue are removed by autolysis and by phagocytosis. The proliferating endothelial sprouts join with one another, and eventually continuous channels through the mass of fibrous tissue are established—a process known as canalization of a thrombus. In larger thrombi containing an excessive number of leukocytes, death of these cells and liberation of their enzymes may bring about puriform softening of the centers. The superficial layers are protected by the antitryptic substances in the blood. Some thrombi, especially those in the pelvic veins, undergo organization and final calcification to form *phleboliths*.

body where the circulation is slowest: in the lower extremities, in the appendages of the cardiac atria, and in the cranial sinuses. Thrombi are formed in those regions of the body where there are wide venous channels interspersed with smaller vessels, such as in the veins of the pelvis. Thrombi are more common in the left leg than in the right because the left iliac vein is longer and must pass beneath the right iliac artery to reach the vena cava, and because this vein is at times compressed by a distended sigmoid colon. Finally thrombi are far more common in patients with cardiac failure and in persons who are confined to bed than in persons with a normal circulation or who are up and about.

The role of *lesions* of the vascular wall is exemplified in the occurrence of thrombi in

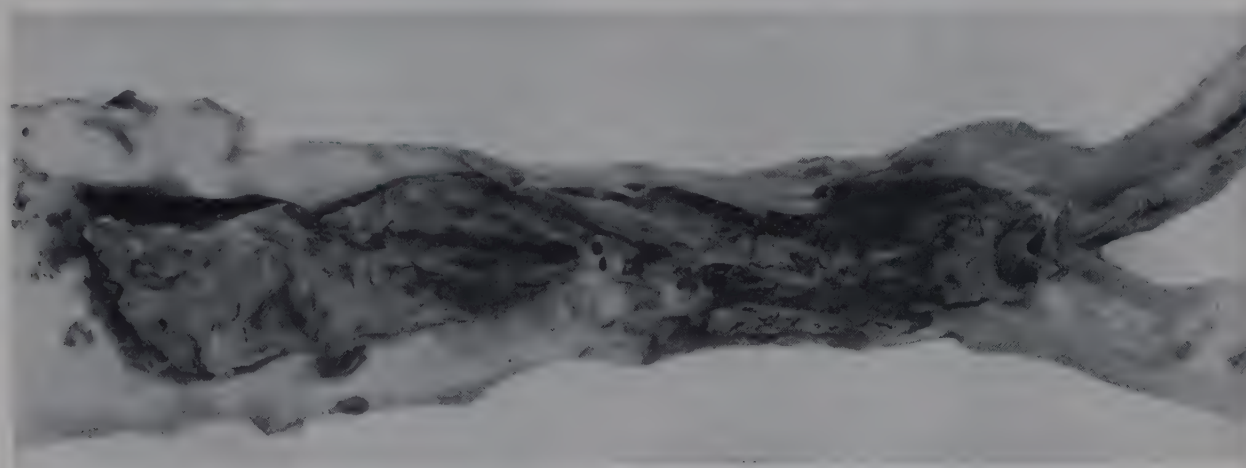


Fig. 45. Partly organized thrombus in aorta.

Causes. The causes of thrombosis may be arranged in three categories: alterations in the blood, mechanical disturbances in the circulation, and lesions of the vascular wall. The influence of *alterations in the blood* is seen in the thrombosis associated with dehydrated states and with polycythemia, both probably related to increased viscosity rather than to any of the elements that cause clotting of blood. There is little question, however, that a decrease of these elements or an increase of the anticoagulation factors such as heparin may prevent the formation of thrombi.

Two *mechanical disturbances* in circulation are related to thrombosis: slowing and eddying of the blood. Thrombi are rare in the arteries where the flow of blood is rapid, and are common in veins. They are likely to form in the valvular pockets, in the slightly distended segments above the valves, and in aneurysms where eddying is to be expected. They are most frequent in those parts of the

regions of trauma and infection, in the thrombi which form over an area of infarction of the cardiac wall, and in thrombi deposited on an ulcerated arteriosclerotic plaque.

That there are other factors may be presumed from the occurrence of thrombi in influenza and in chlorosis.

Use of Anticoagulants. The anticoagulants, heparin or dicumarol, are used in the thrombo-embolic conditions, especially coronary thrombosis and phlebothrombosis of the lower extremity. In most patients there is benefit without untoward effects, but in a few there are large or small hemorrhages in the viscera (Olivin).

Emboli and Embolism

Embolism is the impaction in some part of the vascular system of any undissolved material brought there by the blood or lymph current. The transported material is an embolus (Welch).

Varieties of Emboli. Emboli may be solid, liquid, or gaseous. The usual form is a piece of a thrombus, and it is customary to call this variety an "embolus," without a qualifying adjective. Other sorts always qualified include fragments of arteriosclerotic plaques, bits of tissue, parenchymatous and tumor cells, parasites, globules of fat, bubbles of air, granules of pigment, foreign bodies, and clumps of

patent foramen ovale or ductus arteriosus—so-called *paradoxical* or *crossed embolism* may occur. An embolus found in the systemic arteries must originate on the left side of the heart or in the arteries, or be a paradoxical embolus.

It is at times difficult or impossible to distinguish between a thrombus and an embolus. A large embolus may be identified by the

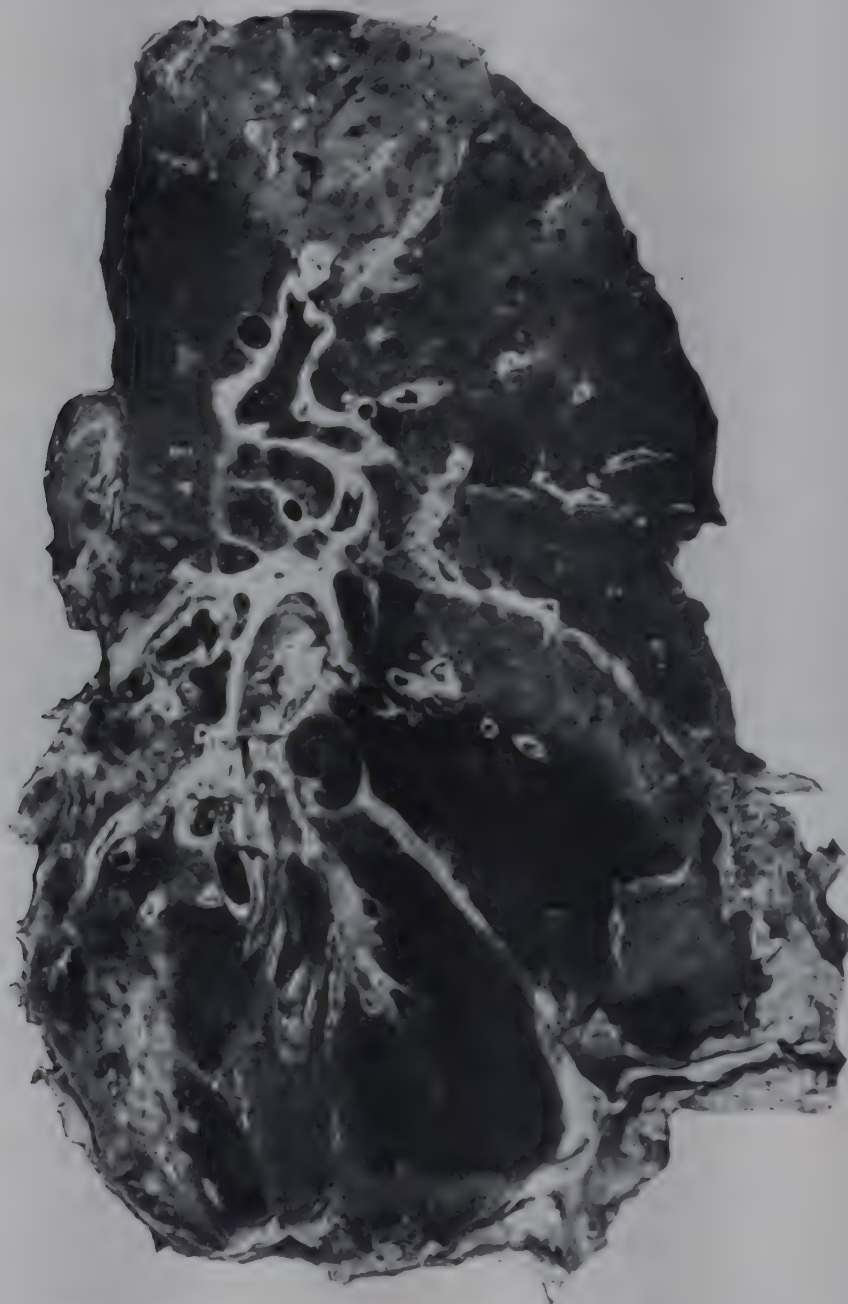


Fig. 46. Pulmonary emboli with early infarct.

bacteria. All emboli free of bacteria are called "bland." Of these the most important are thrombi, air, and fat.

Thrombotic Emboli. As most emboli are carried by the blood, it follows that they are rarely found except in the pulmonary or systemic arteries and in the portal vein. The finding of an embolus in systemic veins implies that it travelled against the flow of blood—*retrograde embolus*. This is seen in the hepatic veins, in which there is at times a reversal of flow. If there is a short-circuit between the right and left sides of the heart—

presence of valvular markings or by a shape which is inconsistent with the structure of the vessel in which it is found. For a day or so after impaction an embolus is not adherent to the wall and thereby differs from a thrombus. If a vessel is completely occluded, a secondary thrombus forms, and within a few days the smaller central embolus may be unidentifiable.

Special types of embolism—pulmonary, renal, splenic, and mesenteric—are discussed in other chapters.

Fat Embolism. Under certain conditions fat

droplets larger than the diameter of the capillary vessels may enter the circulation and be carried to all the viscera. The pathologic changes vary with the time interval between the impaction of the emboli and death. Early there is little more than the presence of fat in small capillary vessels, as shown in frozen sections stained with sudan III. After a period of some hours there are the beginning changes of miliary infarcts. In the lung there are small hemorrhages in the tissues and into the alveoli. In the brain there are hemorrhage and

occlusion of the pulmonary and the cerebral circulation, appearing a few minutes to five or six days after the injury. The circulatory disturbance in the lung is manifested by dyspnea and hypernea, and in the brain by clouding of the sensorium and by coma (Groskloss).

Air Embolism. Pallor, tonic and clonic convulsions, temporary blindness, and coma occasionally develop during operations on the neck or thorax, or during induction of a pneumothorax. The brain at autopsy reveals

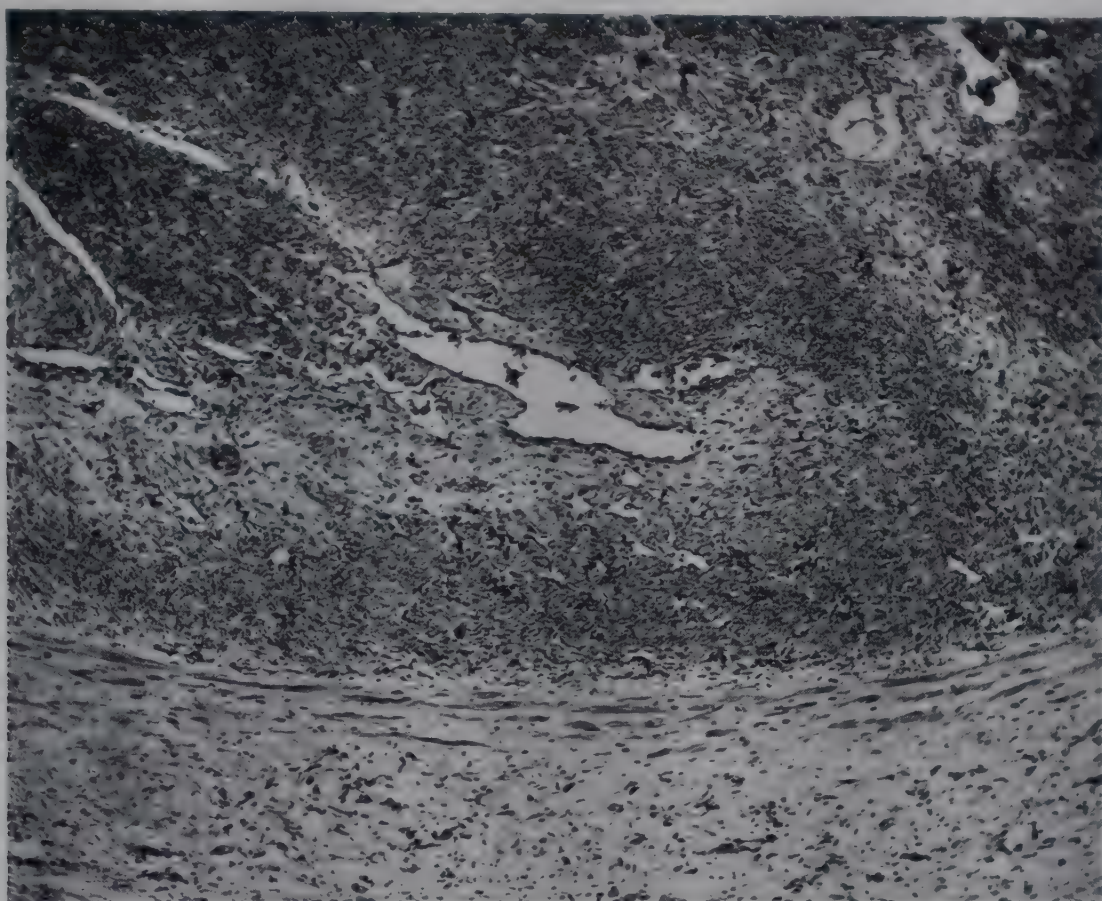


Fig. 47. Organization of a thrombus.

foci of softening. In the kidneys, liver, and spleen infarcts do not ordinarily form, but there is dilatation of the vessels and intense hyperemia.

Causal Factors. Aside from the inadvertent injection of an oily solution into a vein, fat embolism is seen following trauma to a tissue rich in fat under conditions that allow an increase of pressure at that point. Thus a fractured long tubular bone with disruption of the fatty marrow and increase of pressure because of the hemorrhage and edema is one of the most common sites of origin. Similarly a surgical incision through the abdominal wall of an obese person, with subsequent closure of the incision, may lead to fat embolism.

Clinicopathologic Correlation. The signs and symptoms are those of multiple vascular

numerous small air bubbles in the cerebral vessels and hemorrhage into the surrounding tissue. Occasionally the right or left ventricle is filled with a frothy mixture of air and blood and is dilated. It is assumed by some that air is sucked into a cut vein and carried by the circulation into the brain, but others are not impressed with the concept of air embolism, and call the clinical syndrome pleural shock. There is no doubt that an occasional case of air embolism is seen, since the air has been demonstrated in radiographs (Chase). On the other hand, many diagnoses of air embolism made clinically to account for sudden death cannot be substantiated, and a careful autopsy should be performed to rule out other significant diseases. In experimental air embolism, an associated prompt vasoconstrict-

tion and delayed vasodilatation and stasis play as much of a role in inducing the anoxia as do the air bubbles.

The Effects of Thrombosis and Embolism. Infarcts and Infarction

If the artery to all or part of an organ is blocked by a thrombus or embolus, and there is not an adequate collateral circulation, the tissue supplied by this vessel will undergo infarction. The lesion is designated as an "infarct." Rarely infarction results from occlusion of veins or from advanced stenosis of an artery.

Organs possessing an abundant collateral circulation are rarely the site of infarcts—bone, voluntary muscle, skin, thyroid, uterus,

microscopically by loss of nuclei and of cell membranes, with preservation of the general architecture and outlines of the tissue elements. At the edge of the infarct there are numerous polymorphonuclear leukocytes, the nuclei of many of which are undergoing karyolysis. In the immediately adjacent living tissue there are fatty degeneration and storage of glycogen. In most organs the tissue just beneath the surface for a distance of 1 to 3 mm. is adequately nourished by a collateral circulation, and does not undergo necrosis. Within a few days there is beginning proliferation of fibroblasts and blood vessels, removal of the dead tissue, and replacement by a scar. The period required for complete healing of an infarct depends on size, but varies from one to eight months. In the brain the

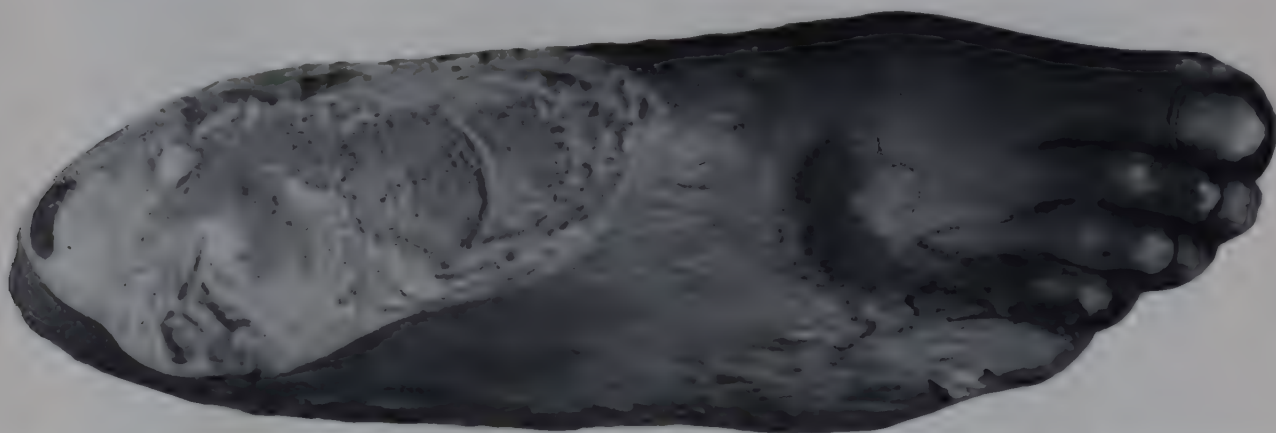


Fig. 48. Gangrene of foot. Note the discoloration and sharp line of demarcation.

and liver. Infarction is the regular result of occlusion of vessels to the spleen, the kidney, brain, retina, and intestine.

Pathologic Anatomy. The initial change noted following occlusion of an artery is local dilatation of the vessels with the passage of a fibrinous transudate into the interstitial spaces. Within a few hours the stagnant blood within the vessels clots, and there is diapedesis of the red cells into the surrounding tissue. In twenty-four to forty-eight hours there is grossly evident necrosis of the coagulation type, and the typical picture of a conical, dry, swollen infarct is produced. In the surrounding tissue for a distance of 1 or 2 mm. there is hyperemia. If the infarct reaches a serous surface there is a fibrinous exudate on the serosa. The firmness of an infarct is caused by coagulation of the proteins and of the exuded fibrin. If an organ has a low protein content, such as the brain and spinal cord, the infarct is soft and liquefies rapidly. Coagulation necrosis is characterized

large amount of fat liberated is phagocytized by gitter cells.

In the lung apparently other factors are necessary for the formation of an infarct beyond occlusion of a branch of the pulmonary artery, which alone leads only to temporary local hyperemia. If, however, there is concomitant passive hyperemia or pleural effusion, or if the embolization is extensive, there is generalized impairment of pulmonary circulation, and infarction follows.

Hemorrhagic and Anemic Infarcts. Infarcts of the brain, lung, and intestine are usually dark red, and are designated as *hemorrhagic*; while infarcts of the kidney, heart, and spleen are pale and are known as *anemic infarcts*. There is microscopic hemorrhage in all infarcts, and hence this distinction is quantitative rather than qualitative.

Gangrene. In an extremity not in contact with living tissue on all sides, the process of necrosis following occlusion of an artery proceeds in a different way, i.e., gangrene. The

tissue deprived of blood supply becomes dehydrated by evaporation of water, and appears as a firm, shriveled, dry, dark red mass.

Clinical Significance. In most infarcts there is pain, produced either by swelling of the tissue and irritation of the nerve endings in and about the region of necrosis, or by the inflammation of the serous membrane over the infarct, as in the lung, heart, and spleen. The presence of necrotic tissue in the body may provoke a slight fever and leukocytosis. Functional disturbances are variable. Occlusion of the main pulmonary artery leads to death within a matter of minutes, and an infarct does not form. Occlusion of the smaller branches of the pulmonary arteries may produce transient dyspnea, but this is rarely excessive. Thrombosis or embolism of a coronary artery may cause immediate death or an infarct may form after some days. A cardiac infarct may impair the ability of the heart to carry the circulation, or it may rupture, with resulting cardiac tamponade. Infarcts of the kidneys are usually associated with slight hematuria, but rarely with any diminution in renal function. In the brain there is a loss of function of the infarcted part. As infarcts are most common in the distribution of the middle cerebral artery, they cause loss of volitional control of one half of the body—hemiplegia.

Reactions Following Transfusions

Transfusion of blood, either fresh or banked, will in about 5 per cent of patients evoke one of four types of reaction: fever from pyrogenic substances, an allergic reaction from an antigen, circulatory embarrassment from too rapid administration (page 72), and a hemolytic reaction from intravascular hemolysis (Flink).

If the transfused blood is of another type, a fatal hemolytic or agglutinative reaction may result, with immediate death or a delayed death on the fourth to the eighth day. In the latter type there is a progressive decrease of urinary output and death results from uremia. The kidneys are enlarged and hyperemic. Microscopic examination reveals edema of the interstitial tissue, degeneration of the epithelium, and filling of the tubules with casts of hemoglobin. Granules of hemosiderin may be present in the epithelial cells (Goldring and

Graef). If the urine is alkaline in reaction the casts of hemoglobin do not form, and this is the basis for treatment of such patients with alkalis. Changes in other organs are inconspicuous. In rapidly fatal hemolytic reactions, a hyperpotassemia by liberation of potassium from the red cells is possible (Wener, Stansfield, Hoff, and Winter).

It is generally considered that the transfusion of pooled plasma does not lead to reactions of the type described, although it is possible for the concentration of antibodies in a single specimen of plasma to be high enough to agglutinate the cells of the recipient. Most reactions following transfusions of plasma are of the anaphylactic type, and are related to the transfer of some antigen from the donor to which the recipient is sensitive. A specimen of the transfused plasma or blood and of the recipient's plasma should be saved to carry out a Prausnitz-Küstner reaction (Lund and Hunt).

Myohemoglobinuria

Myohemoglobin is one of the proteins of muscle and constitutes about one-fourth of the hemoglobin in the body. It is distinguished from blood hemoglobin by spectroscopy (Kreutzer, Strait, and Kerr).

Myohemoglobin may appear in the serum and urine after crushing injury to muscles, after ingestion of certain chemicals, and as a spontaneous disease. Pathologic changes in the latter type are indefinite.

The hemoglobin in march hemoglobinuria may be derived from muscle rather than blood.

Sludged Blood

In a wide variety of pathologic conditions, the red cells, as observed in vivo, agglutinate and form masses which pass through the capillaries with difficulty or block them. The phenomenon has been called "sludged blood" (Knisely, Bloch, Eliot, and Warner).

The significance and importance of this change in the fluidity of the blood has not been fully evaluated. Certainly the flow of blood is partially blocked and some of the agglutinated cells are later destroyed. If the process occurs with most illnesses there could

well be a summation effect which is not now recognized.

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IX

Disturbances in the Growth and Differentiation of Cells

As the metazoan embryo develops, it becomes a complex animal organism with a diversity of cells, tissues, and organs. In adulthood, the cellular structure and organization are maintained on a plateau of growth and functional activity. With the approach of old age, there is a progressive loss of structural elements. Thus we might think of the anatomic life of a single animal organism as being composed of three essential parts, a first period of evolution, a second period of static maintenance, and a third period of involution. The pathologist is concerned with different problems in each of these periods.

During evolution, the processes of cellular proliferation, cellular movement, cellular differentiation, organogenesis, and correlative adaptation may be blocked or perverted. The result is a teratoid monster, or a congenital anomaly, depending on the amount of tissue involved (see Chapter LXXIII, p. 582).

The adult phase of life, from the cessation of growth and development to the beginning of involution, is characterized by a maintenance of normal structure and function. Some cells and tissues, such as the epithelium of the skin and the red blood cells, are constantly destroyed and replaced. Other cells and tissues only proliferate in response to injury or a demand for increased functional activity—parenchymal cells of the liver and kidney. Still other cells are incapable of proliferation, and loss of one of them is irreparable—nerve cells and muscle cells.

During involution the processes may be accelerated—premature senility; or they may be less active than normally—delayed senility. A third possibility is an inequality in the involution of different organs, as exemplified in presenile atrophy of the brain.

To the morphologist, the changes in growth and differentiation of cells may be classed in

one of three categories: alterations in size, alterations in number, and alterations in type. A decrease in the size of a cell or organ, or a decrease in the number of cells, is *atrophy*. An increase in the size of a cell or organ is *hypertrophy*. An increase in the number of cells is *hyperplasia*, and a change in the type of an adult cell is *metaplasia* (Bloom; Weiss).

Atrophy

Atrophy is a decrease in the size of a part of the body, of an organ, or of the individual cells of a tissue or organ; or a decrease in the number of cells in an organ or tissue unit. It differs from *hypoplasia*, which is congenital smallness. In order to avoid confusion the term “atrophy” is not ordinarily applied to a decrease in the size of an organ or tissue produced by inflammatory destruction or necrosis and fibrous replacement.

Pathologic Anatomy. The outstanding characteristic of the atrophic organ is smallness, in both volume and weight, in some instances as low as 30 per cent of the normal. The tissue is flabby but firm, and varies in color from normal to dark brown, depending on the associated deposition of pigment. The covering membrane, skin, or serous surface is loose, wrinkled, and frequently slightly thickened. In some structures such as skeletal muscle and pancreas there is an increase of fat tissue which separates the small parenchymal elements. In the skin elastic fibers are lost, and consequently turgor and elasticity decrease. If vessels course over the surface of the organ they may appear tortuous, as a consequence of the decrease in the length of tissue over which they pass. Atrophy of the brain is characterized by a decrease in the size of the convolutions and widening and deepening of the sulci.

Microscopic examination shows one or both of two changes: decrease in number of cells or units, and decrease in the size of the cells. The cytoplasm of the cells is dense and is frequently filled with granules of a brown pigment. The nuclei are small and hyperchromatic, and have a wrinkled, nuclear membrane. In some organs there is a slight increase of the supporting tissue, either fibrous or glial. In the heart the pigment character-

this is an increase in the activity of the intracellular autolytic enzymes, notably cathepsin. On the basis of numerous studies of autolysis in vitro, Bradley believes the steps in vivo are as follows: a diminution in oxidative metabolism, increased production and accumulation of acids which raise the hydrogen ion concentration and activate the protein substrate, associated high levels of protein sulfhydryl and reduced glutathione which in-

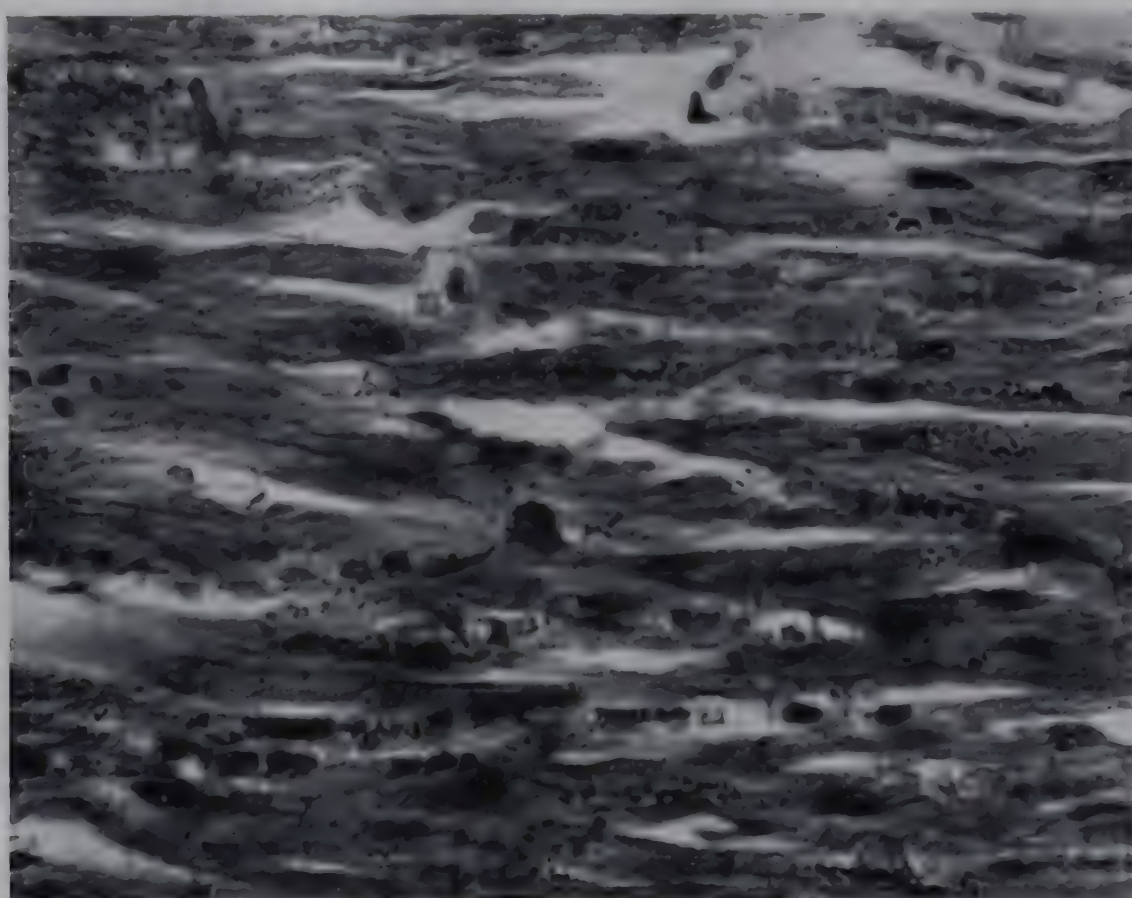


Fig. 49. Brown pigmentation of the myocardium. The granules of pigment are about the poles of the nuclei.

istically forms a cap about the ends of the nuclei.

Causes of Atrophy. The ultimate cause of atrophy is probably some single defect in metabolism, but in practice it is seen under a wide variety of conditions: in emaciated states; in organs with an end artery circulation when there is some disease that restricts the minute-volume flow of blood; in pressure from surrounding rapidly growing tumors or from dilatation of the ducts within a hollow viscus (pressure atrophy); after section of nerves supplying a muscle or when the muscles are not used (neurotropic and nonuse atrophy); in old age (senile atrophy); and in specific organs where there is a deficiency of hormonal stimulation (hormonal atrophy).

Chemical Pathogenesis of Atrophy. Reduction in the number and decrease in the size of cells predicate a loss of preexisting protoplasm. The only known chemical process for

crease the proteolytic activity and range, and removal by dialysis of the cleavage products so that the reaction may be completed.

Hypertrophy and Hyperplasia

The processes, hypertrophy and hyperplasia, are so closely related that they may well be considered together. For example, in hypertrophy of the kidney following unilateral nephrectomy, there is both proliferation of the cells of the tubules and glomeruli—hyperplasia; and an increase in the size of each nephron—hypertrophy. On the other hand, in hypertrophy of the heart, there is no increase in the number of myocardial nuclei per unit of tissue, hence this is a pure hypertrophy.

Pathologic Anatomy. The hypertrophic or hyperplastic organ is increased in size from a

few per cent to over 400 per cent, as determined by volume or weight. A heart normally weighing 350 gm. may increase in weight to 1200 to 1400 gm. The organ is typically of normal consistency and color. Features observable microscopically in hypertrophy include an increase in the size of the individual cells and sometimes alterations in the size of the nuclei. Thus in hypertrophy of the heart, the fibers are increased in diameter and the nuclei are larger and tend to be square-ended (Karsner, Saphir, and Todd). In hypertrophy

moved in five-day-old rats, the opposite kidney increases in weight in forty days to 65 per cent above the normal, while similar experiments in 540-day-old rats show only a 25 per cent increase (MacKay, MacKay, and Addis). Despite the increase in weight, there is no increase in the number of nephrons (Moore and Hellman). In contrast, hypertrophy of the surviving organ after unilateral adrenalectomy, oophorectomy, and orchiectomy is not influenced by the age of the animals (Addis and Lew).

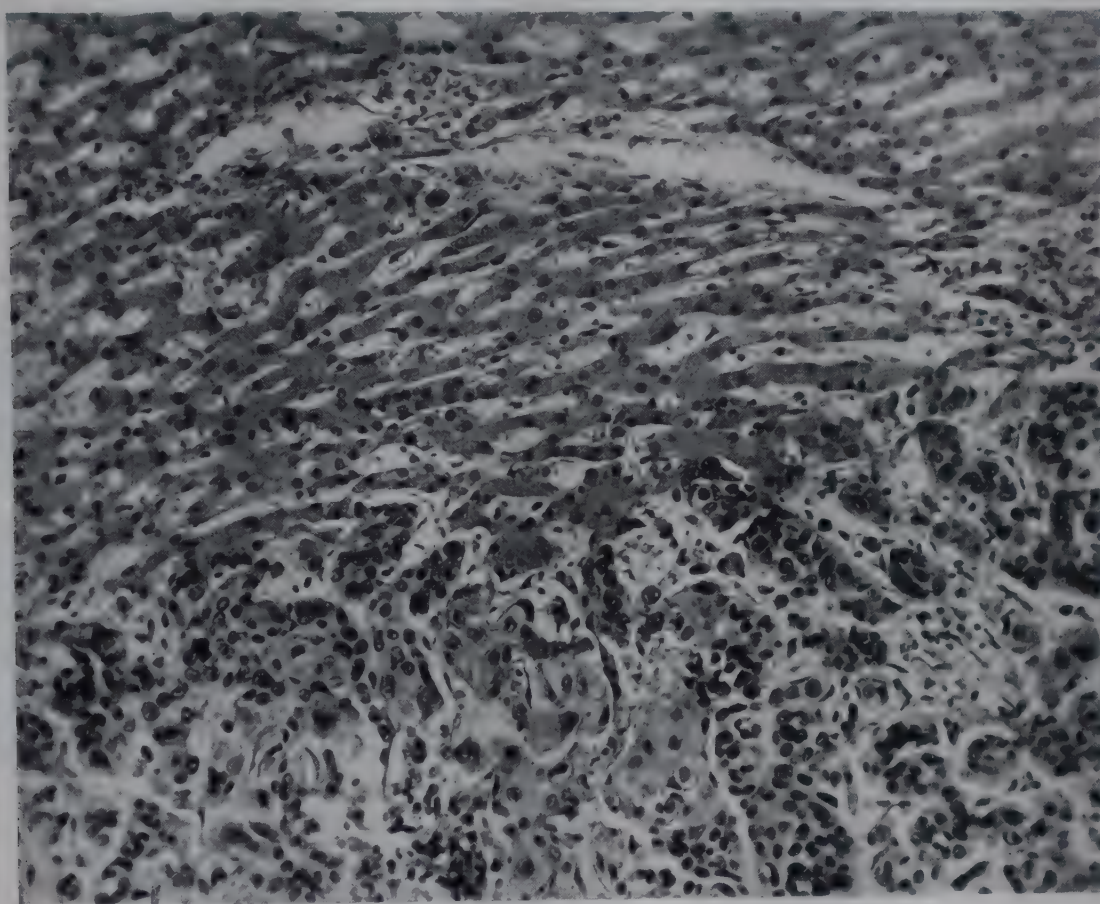


Fig. 50. Pressure atrophy of the hepatic cells about a rapidly growing metastatic carcinoma of the liver.

of a tissue unit such as a glomerulus, there is an increase in the number of cells. The microscopically demonstrable criteria of hyperplasia are an increase in the number of fixed tissue cells per unit, a disproportion between the size of an organ or unit and size of the component cells, and the presence of cells in mitosis.

Factors Controlling and Limiting Hypertrophy and Hyperplasia. Both hypertrophy and hyperplasia are the reaction of cells to an adequate stimulus and the formation of new cytoplasm. It follows that many factors may influence the qualitative and quantitative response.

Age. The influence of age is well shown in the hypertrophy of the remaining kidney after unilateral nephrectomy. If one kidney is re-

Cellular Type. Different cells and organs have a different capacity to undergo hypertrophy and hyperplasia. Adult nerve cells and muscle cells cannot increase in number, while many epithelial and mesenchymal derivatives have great potentialities to increase in both number and size. After removal of a part of an organ, the percentage of restoration of the preoperative weight of the entire organ in a period of forty days in a few representative tissues is: liver 100 per cent, kidney, adrenal, and ovary 70 per cent, testis 55 per cent, and prostate inappreciable (Addis and Lew).

Nutrition. Since hypertrophy and hyperplasia consist of an increase of cytoplasm, it follows that there must be an adequate supply of nutritive substances in the diet. The rate of proliferation of fibroblasts in healing

wounds is decreased if there is not a minimum amount of protein in the diet (Thompson, Ravdin, and Frank). Similarly, restricted consumption of protein decreases the total restoration and the velocity of restoration of the kidney, adrenal, and ovary after unilateral removal (Addis and Lew).

Blood Supply. Closely related to the adequacy of dietary elements is the total flow of blood to the parts, so that the cytoplasmic building-stones may be available to the growing tissue. There is some evidence that an organ served by arteriosclerotic vessels is not as capable of hypertrophy and hyperplasia as an organ supplied by normal vessels.

be increased to the same extent as it can be in a normal heart. It is possible that this decreased reserve strength is limited by other factors, such as the blood supply.

Causes of Hypertrophy and Hyperplasia. If considered superficially, there are apparently many causes of hypertrophy and hyperplasia, but in the ultimate analysis there is probably only one physiologic stimulus: an increased demand for work in terms of greater muscular activity, increased secretory activity, or an increased output of cells.

The somatic muscles of the athlete and of the laborer are larger. The heart of the person with hypertension or with chronic valvular

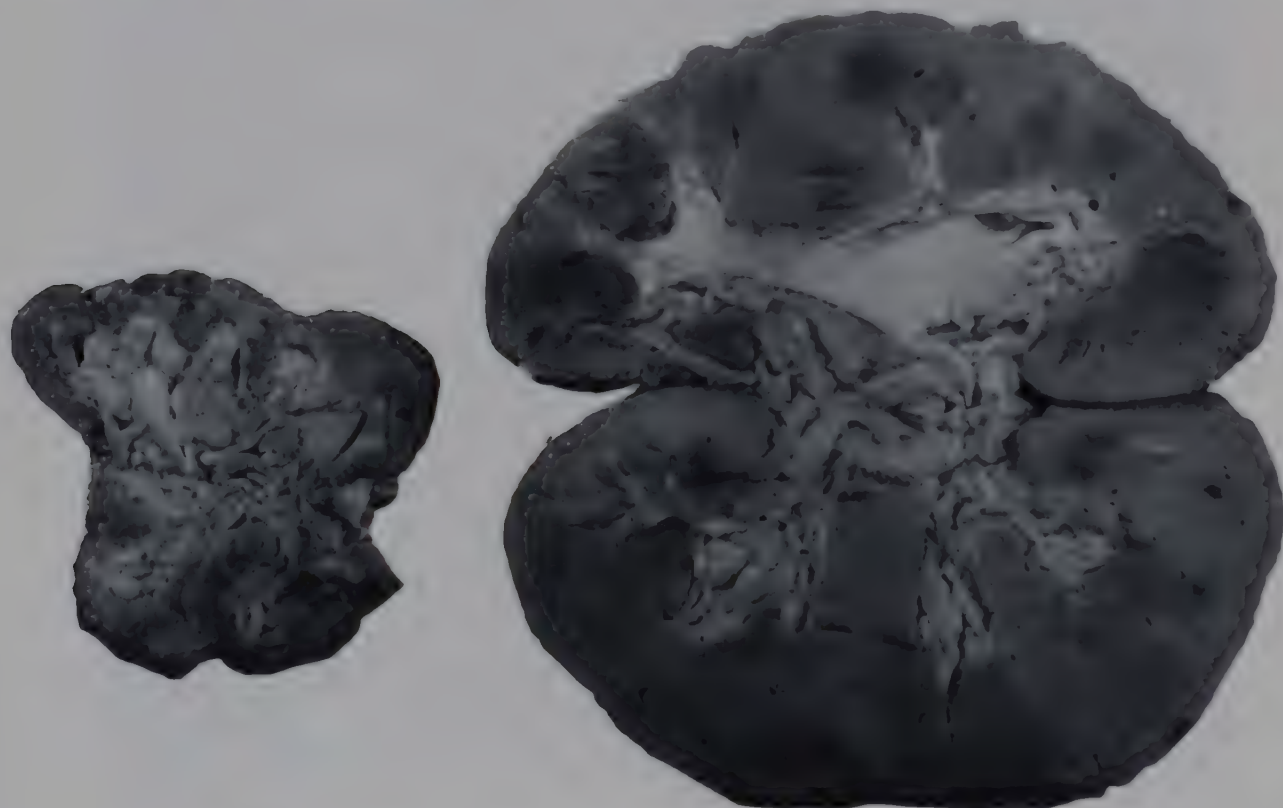


Fig. 51. Atrophy of one kidney and hypertrophy of the other.

Functional Capacity in Hypertrophy and Hyperplasia. A greater mass of cytoplasm either within existing cells or in an increased number of cells would, in general, have an increased capacity to do work. In most organs this can be demonstrated. Within a few weeks after unilateral nephrectomy in dogs and rabbits, the single kidney has a functional capacity in response to both a normal load and an overload equal to that of both kidneys (Karsner, Hanzal, and Moore). In semispayed rats, the onset of ovulation, the regularity of the cycle, and the fertility are not influenced, despite the fact that the number of ova in the surviving ovary is not increased (Arai). On the other hand, the hypertrophic heart has a decreased functional capacity per gram of tissue, since the minute-volume output cannot

disease is increased in weight. The uterus of the pregnant woman is increased in size and weight. The stimulus in all, expressed physiologically, is preloading and afterloading or, in simple terms, stretching of the muscles.

The surviving tissue, after removal of a part of an organ, is called upon to perform functions formerly carried out by a larger amount of tissue. The 150 gm. of renal tissue in one kidney, after removal of the other, has all the metabolic products brought to it for excretion. In other words, it is preloaded and afterloaded in exactly the same way muscle is.

In some instances, the analysis can be carried beyond the broad physiologic phenomenon of increased demands. Hypertrophy and hyperplasia in organs susceptible to hormonal action can be reproduced experimentally. The

ducts of the breast in pregnancy and in lactation increase in number and size as the result of the action of hormones. Similarly, hypertrophy and hyperplasia of the thyroid is caused by stimulation by the pituitary. It is probable that further study will reveal a chemical mechanism for all types of hypertrophy and hyperplasia.

must await further investigations, but the minute-volume flow of blood to the organ is undoubtedly one of the important limiting factors. A second important factor is the capacity of the cell to respond. For example, with moderate doses of androgen, the epithelial cells of the prostate will increase proportionately in size and number, but beyond a



Fig. 52. Anatomy of the muscles of the leg drawn by Leonardo da Vinci. (After Garrison.)

Limit of Hypertrophy and Hyperplasia and Functional Failure. If the stimulus for hypertrophy and hyperplasia is an increased demand for work, and if there are intrinsic and extrinsic factors which limit the degree of response, it is logical to believe that a point will be reached where the capacity to respond can no longer equal the demand. At this point the organ will fail functionally. In one person a heart fails after it reaches a weight of 500 gm., while in another, functional inadequacy is not evident until the heart weighs 1000 gm. An understanding of these differences

certain point no amount of androgen will cause a further response.

Chemical Pathology. Little is known of this subject, but it seems probably that the basic mechanism is the opposite of that discussed under "Atrophy."

Metaplasia

Metaplasia is a change in the cellular type of adult cells to a form not normally present in that tissue. The characteristic epithelial lining of the bronchi and ducts of most glands is

columnar in type. If this changes to squamous, it is designated as "metaplasia." Similarly, there is normally no cartilage or bone in the subcutaneous tissues or in the viscera. But in pathologic conditions either or both may be present. The process by which cartilage and bone are formed is metaplasia, and the lesion is designated as heterotopic cartilage and heterotopic bone.

Causes of Epithelial Metaplasia. Metaplasia of epithelium, most commonly from cuboidal or columnar to squamous types, is seen in

ful study of wounds shows a significant number of small spicules of bone. Heterotopic formation of bone in muscles frequently follows trauma with secondary hemorrhage.

Mechanism of Metaplasia. There are two possible origins of the metaplastic cell: direct, by transformation of one adult cell into one of another type, and indirect, from more primitive cells formed as the normal cells proliferate. The latter mechanism is more generally accepted. In vitamin A deficiency, the columnar cells do not change to squamous

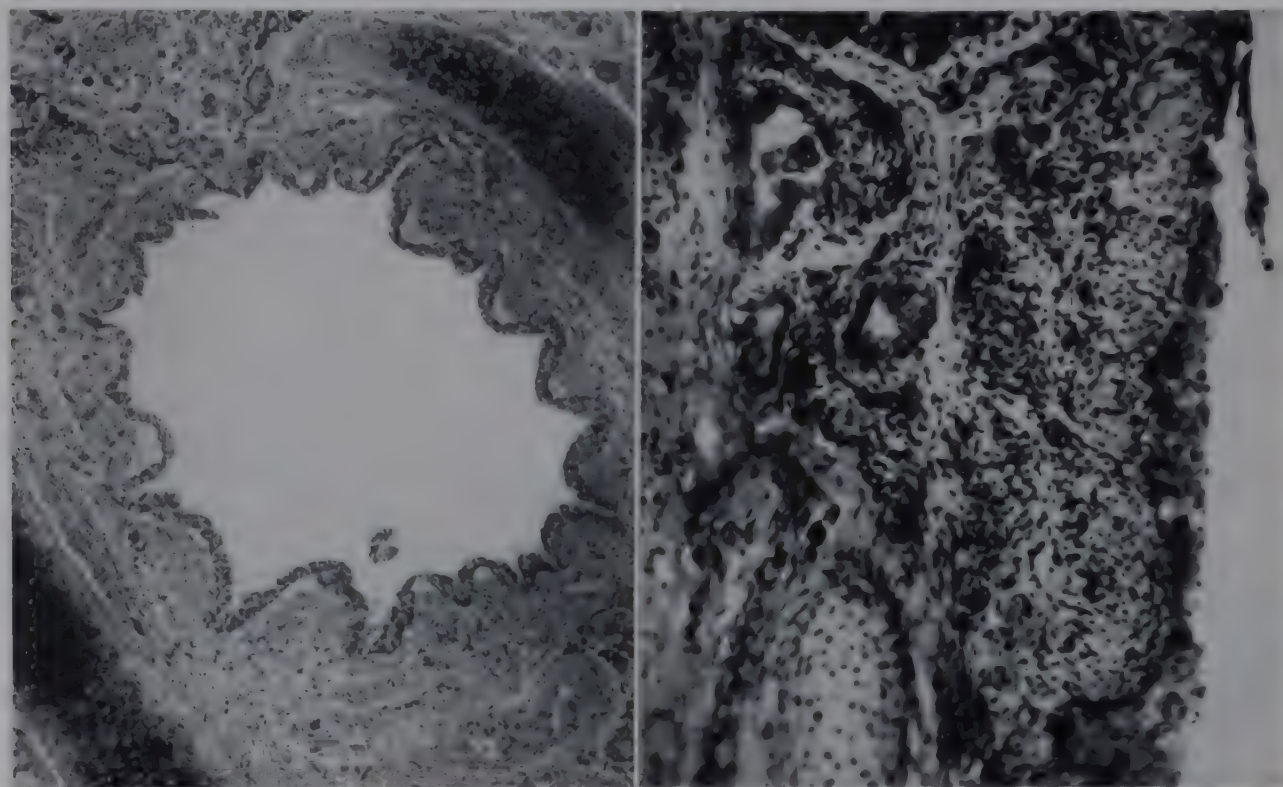


Fig. 53. Metaplasia of the bronchial epithelium to a squamous type in chronic infection of the lung.

association with three conditions: chronic inflammation, rapid growth, and vitamin A deficiency. The best known examples in chronic inflammation are in chronic bronchitis and bronchiectasis and in chronic pyelonephritis. In rapid growth, as in tumors, the cells accumulate more rapidly than they can differentiate and organize. In vitamin A deficiency, there is squamous metaplasia in the ducts of most of the glands and in the urinary tract. Physiologic studies might show that the ultimate cause of all epithelial metaplasia is related to vitamin A dietary deficiency, a block in utilization, or an inadequacy because of rapid growth.

Causes of Mesenchymal Metaplasia. Heterotopic bone and cartilage may form in any lesion in which there is necrosis or proliferation of fibroblasts. Calcification may occur in necrotic tissue, and heterotopic ossification is possible in any focus of calcification. Care-

ful study of wounds shows a significant number of small spicules of bone. In some types of metaplasia, tissue organizers may be operative. Thus chemical substances derived from blood extravasated into muscle may stimulate primitive connective tissue cells to differentiate into osteoblasts. An outstanding example of this influence of one tissue on another is the ossification in connective tissue which follows transplantation of a small piece of the mucosa of the urinary bladder (Huggins).

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X

Inflammation

Long before the days of medicine and the medical sciences man noticed that injury was followed by a definite series of changes in the traumatized tissue. Celsus in the first century A.D. formulated these alterations into what we now know as the cardinal signs of inflammation: rubor, tumor, calor, and dolor; or redness, swelling, heat, and pain. These signs result from two basic local changes in the tissue: increase of vascular supply and increase of extravascular fluid and cells. The increase of vascular supply brings more blood to the part and keeps it in the part for a longer time, hence the redness and increase of temperature. The increase of extravascular fluid and cells in a focal region is responsible for the swelling, and in turn the pressure on the terminal nerve endings by the elevated tissue tension is registered in consciousness as pain. Since inflammation usually leads to impairment of physiologic activity of the part, some add a fifth cardinal sign: *functio laesa*, or disturbance of function.

Causes of Inflammation

Even the most cursory study of inflammation reveals that a wide variety of agents provoke a reaction in the tissues. The problem must be approached from two standpoints: the apparent causes and the ultimate causes.

Apparent Causes of Inflammation. *Living Agents.* The outstanding causes of acute inflammation are micro-organisms: bacteria, viruses, rickettsiae, fungi, and protozoa. The micro-organisms vary in ability to invade the tissues and establish an inflammatory reaction. Thus, many fungi grow on the surface of the skin and produce little or no inflammation in the dermis (see the paragraph on superficial dermatomycoses, p. 414). Some bacteria are normally present in the intestinal lumen; but

if they are implanted in the urinary tract, an acute or chronic inflammation is the result (see Chapter LXXXVII, p. 749, on pyelonephritis). Other bacteria, notably the hemolytic streptococci, vary in disease-producing capacity with the different strains (see Chapter XXI, p. 205, on upper respiratory infections). Still other bacteria, such as the diphtheria bacillus, the dysentery bacillus, and the cholera vibrio, evoke a local inflammation on a mucous surface and a systemic reaction because of the elaboration of an exotoxin or endotoxin.

Physical Agents. A second important category of causes of inflammation consists of physical agents such as trauma and radiant energy. The clean, aseptic incision of the surgeon goes through all the changes of inflammation. A blow to the tissues may injure or kill cells and initiate inflammation. Radiant energy in the form of electricity, ultraviolet rays, infra-red rays, x-rays, and radium rays excites different types of reaction in the tissues (see Part III, p. 474, on diseases caused by physical agents.)

Chemical Agents. Chemical agents include those introduced from without (exogenous) and those elaborated in the body (endogenous). *Exogenous* agents are typified by the corrosive chemicals, such as nitric acid and phenol. *Endogenous* poisons are probably responsible for the toxemias of pregnancy and other diseases. Also classed as chemical agents are the *antigens*, which, if they meet antibodies in the tissue, provoke a severe and characteristic inflammation generally known as "allergic inflammation" (see Part IV, p. 502, on diseases caused by chemical agents).

Ultimate Causes of Inflammation. The ultimate cause of all inflammation is probably the death of a cell or group of cells and liberation of a chemical substance, the nature of

which is at present unknown. Lewis and Grant were impressed with the similarity of inflammation and the response to injections of histamine. They proposed that injury to tissue liberates histamine or an "H" substance which then calls forth the vascular reaction and the increase of permeability. Menkin isolated from exudates a crystalline polypeptide, which he named "leukotaxine." This substance on injection provokes typical vascular and permeability alterations, and according to him is free of histamine. Menkin has also described another substance isolated from

of the blood flow through the part is greatly accelerated. After several minutes to an hour, depending on the severity of the injury, the capillaries dilate. The expansion of the capillary bed is associated with a slowing of the blood stream. In the flowing blood of the normal and accelerated stream the corpuscles, both red and white, are carried in the axial part of the stream, and there is a peripheral zone of clear plasma. As the rapidity of flow decreases the white blood cells settle into the peripheral stream and travel at a slower rate. In fact many of the white cells behave as

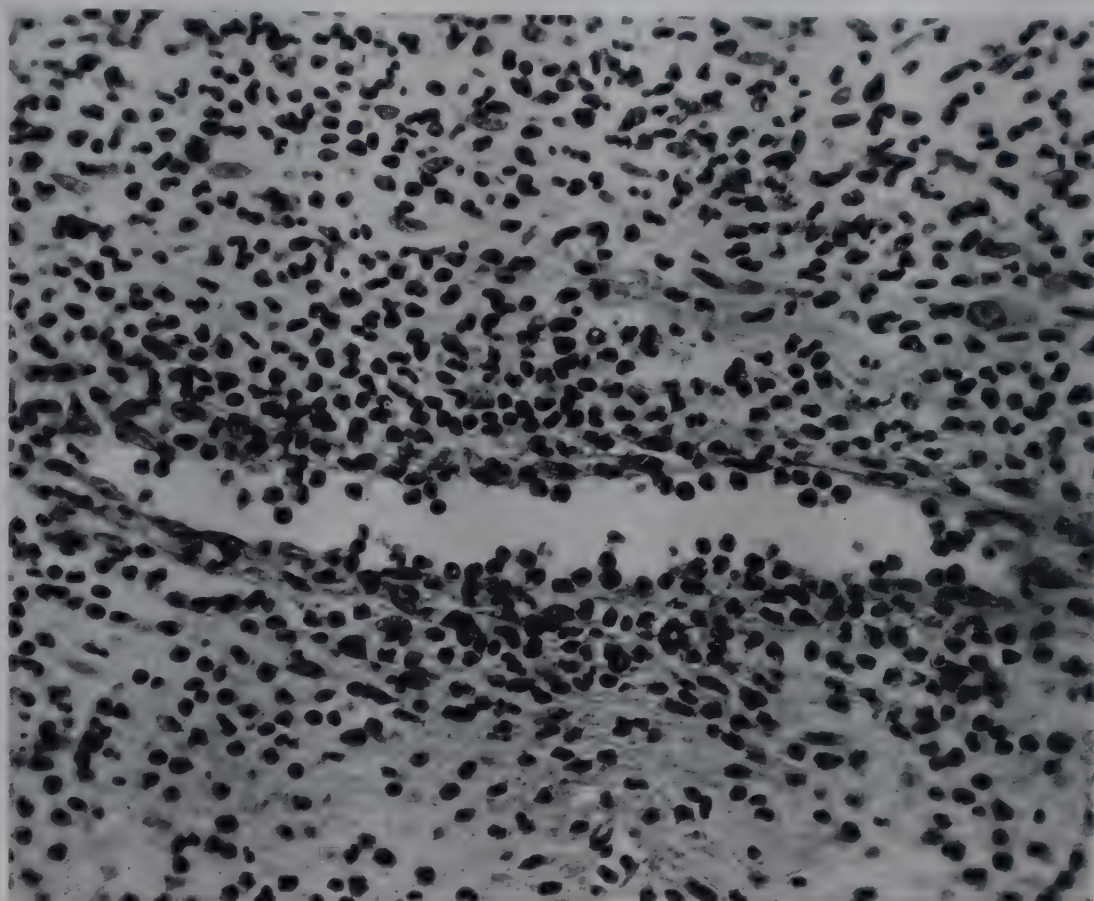


Fig. 54. Margination and migration of leukocytes in acute inflammation.

exudates which causes necrosis. It is unlikely that any one chemical substance is responsible for all of the changes in all types of inflammation (Rous and Gilding). It is possible that local anoxia and an accumulation of the acidic products of metabolism play a role.

Pathogenesis of Inflammation

Vascular Dilatation and Alterations in Blood. The first change in inflammation is generally believed to be transient contraction of the vessels in and about the injured area. Within a few minutes the vessels dilate, first the arterioles and shortly thereafter the venules. As the arterioles dilate, the rapidity

though they were sticky, and pass along in the peripheral stream in an interrupted motion, synchronous with the systole of the heart. Eventually the current slows to the point of stagnation or stasis, and all distinction between the axial and the peripheral stream is lost. The lumen is filled with closely packed red and white cells, and the white cells in increasing numbers accumulate on the endothelial surface.

Exudation and Cellular Migration. As the rate of flow diminishes, a swelling of the tissue and a separation of the cellular elements become apparent—exudation of fluid. The white cells which have accumulated on the inner surface of the endothelium pass through the wall by active ameboid motion

and appear in the adventitial tissues—cellular migration (Fig. 54). The fibrinogen in the exuded fluid gels to form a delicate network of fibrin through the intercellular spaces.

Terminal Changes. If the injury has not been too severe or extensive, the process reaches a maximum in five to eight hours. The injured surface of the skin or peritoneum is covered by a layer of fibrin—the “scab” of lay terminology. The vessels gradually return to a normal caliber, and the flow of blood through the part is reestablished. Some of the

(Kettle). The more important of the specific types of inflammation are serous inflammation, catarrhal inflammation, fibrinous inflammation, pyogenic inflammation, hemorrhagic inflammation, necrotizing inflammation, inflammation associated with an infiltration of eosinophils, inflammation associated with infiltration of lymphocytes and mononuclear cells, and the infectious granulomas.

Serous Inflammation. As the term indicates, serous inflammation is characterized by the focal accumulation of fluid in response to an

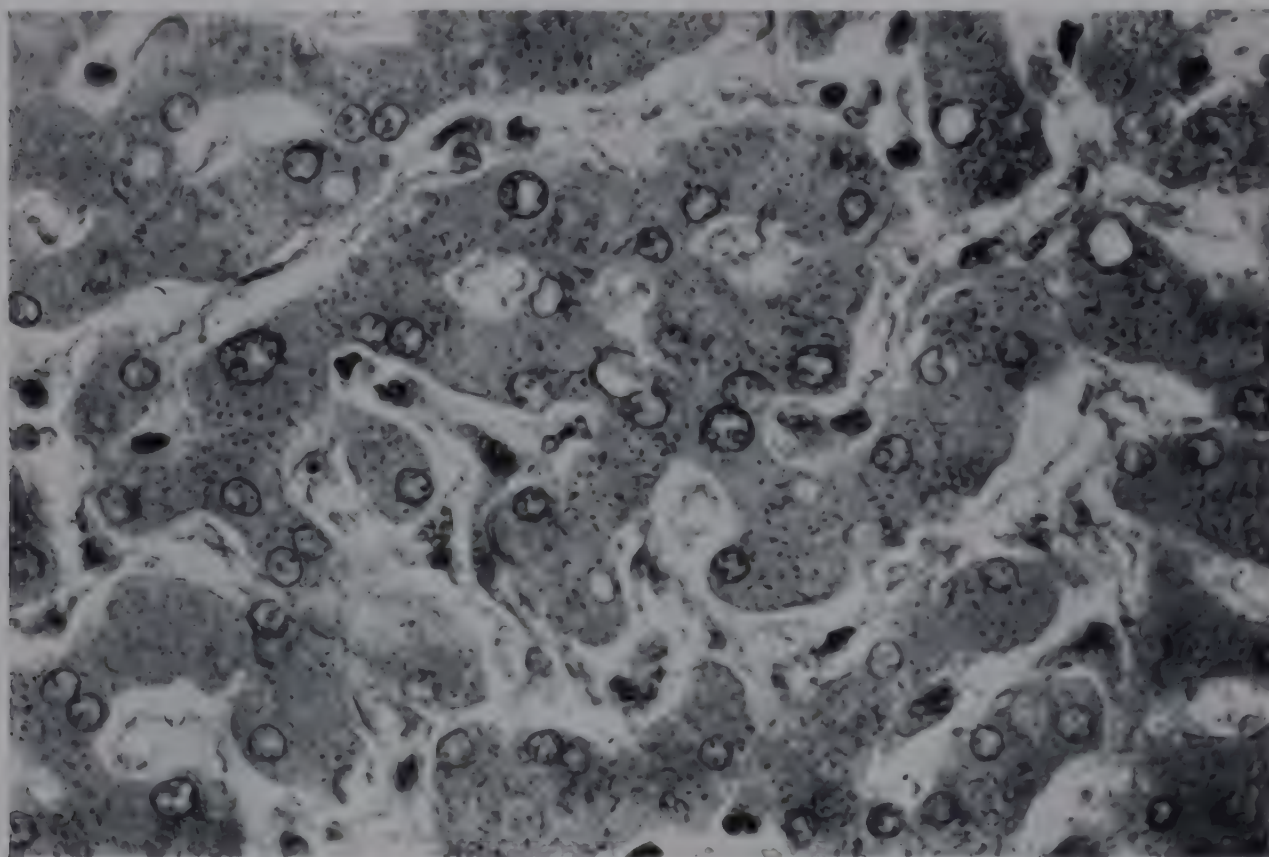


Fig. 55. Serous hepatitis.

leukocytes undergo degeneration, while others reenter the vessels and leave the region. The epithelium or mesothelium proliferates and covers the surface beneath the scab. The excessive fluid is absorbed into the blood and lymph, and the fibrin is digested. In minor injuries the integrity of the part and normal structure and function are restored within twenty-four to forty-eight hours (Adami).

Types of Inflammation—Cells of the Exudate

Most agents producing disease set up local inflammation either at the site of entry into the body or in a tissue of elective localization. The inflammation is in many instances specific, and the pathologist may make a causal diagnosis by a proper evaluation of the gross and microscopic appearance of the tissue

injury. The best-known examples occur in the skin and in the serous cavities. Following minor injury or application of heat to the skin, a blister or vesicle forms within the epidermis or at the epidermodermal junction. The fluid is clear and contains only a few cells. In the surrounding tissue there are hyperemia and edema, but only slight cellular infiltration. In the serous membranes, the pleura, the pericardium, and the peritoneum large amounts of a clear, light yellow fluid may accumulate. The vessels of the peritoneum are conspicuous, but the peritoneal surface is usually smooth and glistening, or only slightly dulled. On removal the fluid may clot.

Less is known about serous inflammation in the solid viscera, typified by so-called “serous hepatitis” (Fig. 55). The endothelial cells of the sinusoids are lifted from the hepatic cords, and in fixed tissue a fine, granu-

lar precipitate is seen in the space between the two. The lesion has been observed in the livers of "healthy" people killed in automobile accidents, and has not been correlated with any other physiologic or pathologic process.

Catarrhal Inflammation. This type of inflammation occurs only on mucous surfaces and is characterized by excessive secretion of mucus. An example known to everyone is the common cold. In this condition after an initial period of a sense of unusual dryness of the

cosa is changed in one or two days to one with discrete or confluent gray patches. The superficial epithelium is in part desquamated, and the membrane is composed of densely packed threads of fibrin and a few leukocytes.

In the serous cavities fibrinous or serofibrinous inflammations are common. The serous surface is hyperemic and covered by a shaggy, dull, granular, dry, easily removable material, 1 to 5 mm. thick. The cavity contains a variable amount of fluid. With minimal fluid the two surfaces, if in motion as in

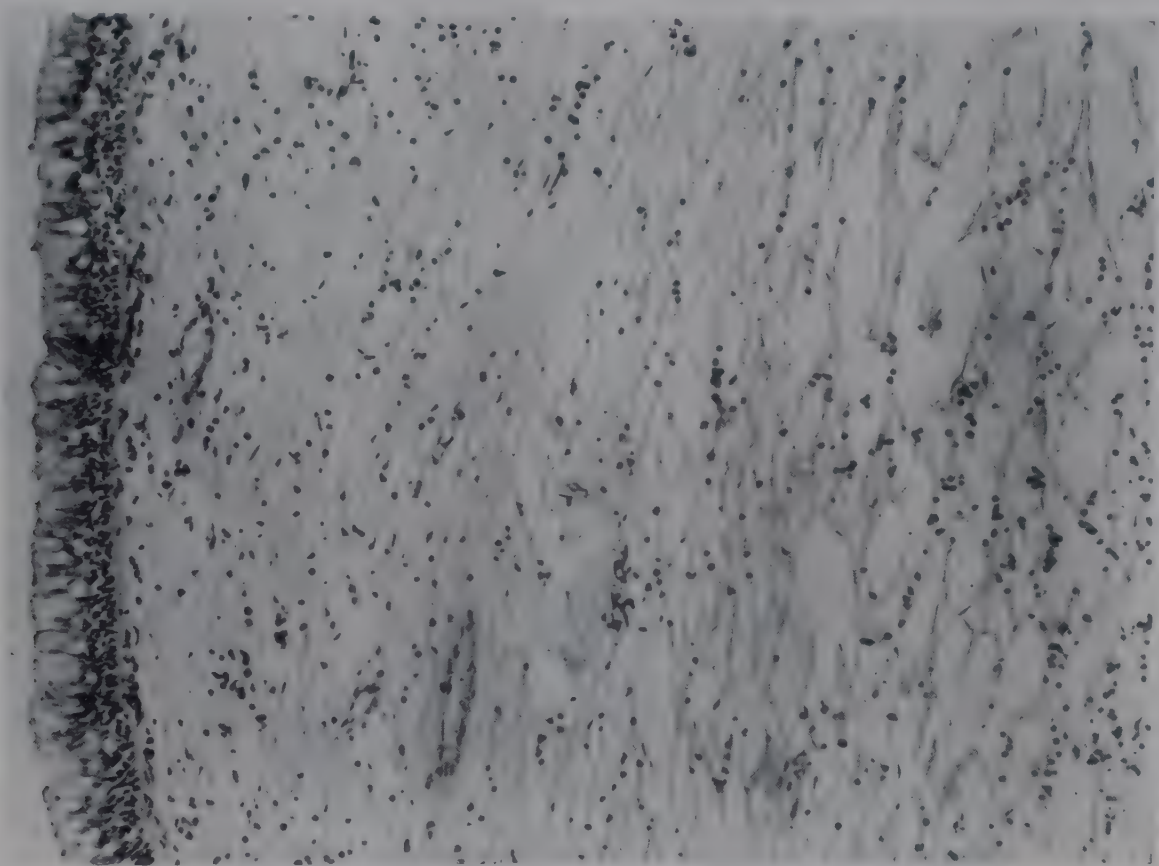


Fig. 56. Catarrhal inflammation in a polyp of the nose.

nose, abundant, clear, viscid mucus is poured into the lumen. Microscopic study in this stage shows edema and hyperemia in the mucosa, distention of the individual cells and the glandular acini with mucus, and covering of the epithelial surface with thick mucus. There are a few cells. Catarrhal enteritis is recognized clinically and pathologically by the presence of large amounts of viscid mucus in the stool.

Fibrinous Inflammation. An inflammation in which the exudate is rich in fibrin is exemplified in diphtheria. From the dilated vessels of the submucosa and mucosa a fibrin-rich fluid is poured onto the surface and quickly clots to form a membrane (hence the term "membranous inflammation"), which appears as a gray area, adherent to the underlying tissue. Thus the early red, swollen mu-

the pleura and pericardium, rub upon one another and produce the friction rub heard with the stethoscope. On the epicardium the fibrin may be whipped into an irregular, villous pattern, sometimes designated as "cor villosum." In all types of fibrinous inflammation there are variable numbers of polymorphonuclear leukocytes or rarely other cells entangled in the threads.

On some mucous surfaces focal or diffuse necrosis of the superficial layers of the mucosa may result in a gross appearance similar to that in fibrinous inflammation. Some apply the term "pseudomembranous inflammation" to this lesion, but it seems better to use the exact designation "necrotizing inflammation" (see p. 100). Similarly the diagnosis "croup" and "croupous inflammation" might well be abandoned.

Serofibrinous Inflammation. An inflammation in which both fluid and fibrin are con-
 ogenic” means “pus-forming.” Pus is defined as a yellowish white, opaque fluid, consisting

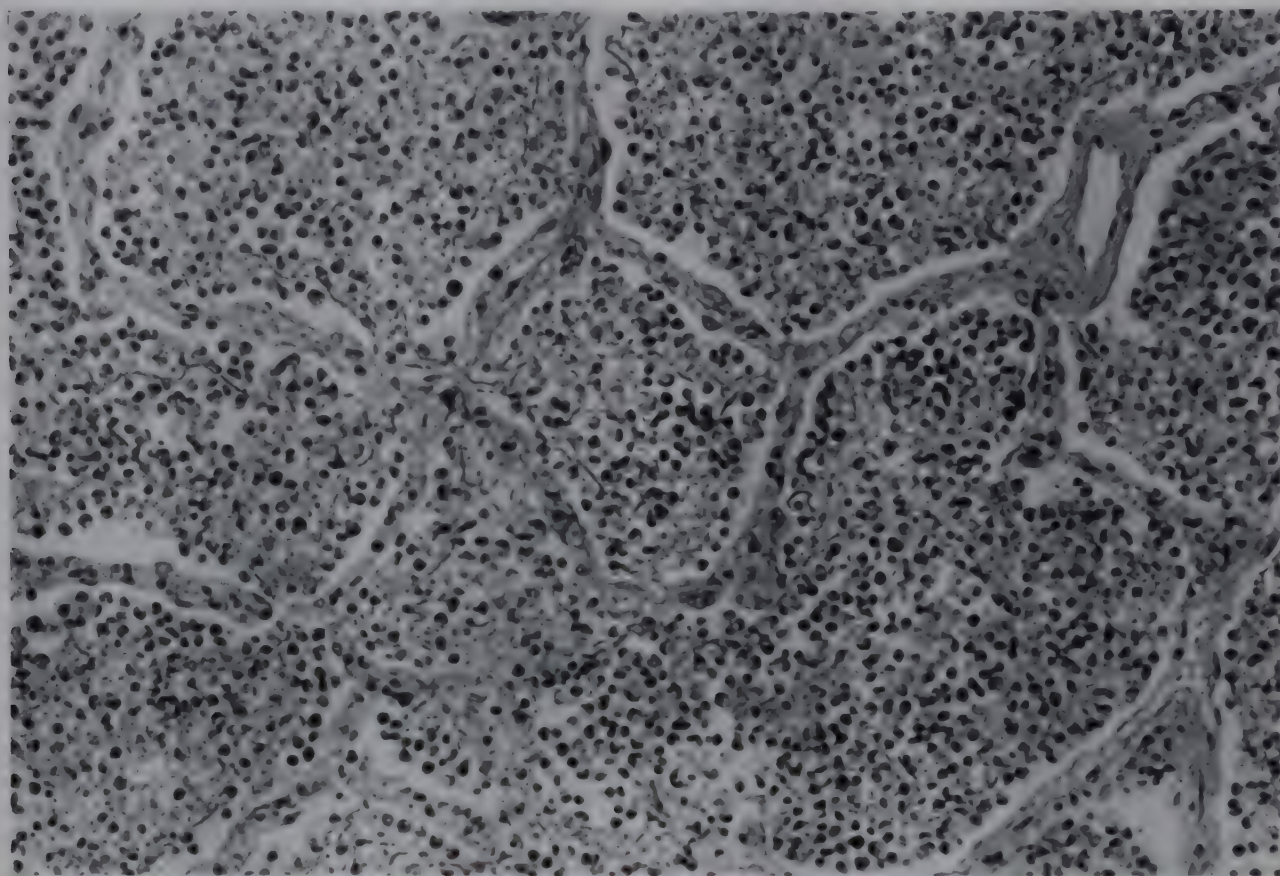


Fig. 57. Fibrinous inflammation (lobar pneumonia).

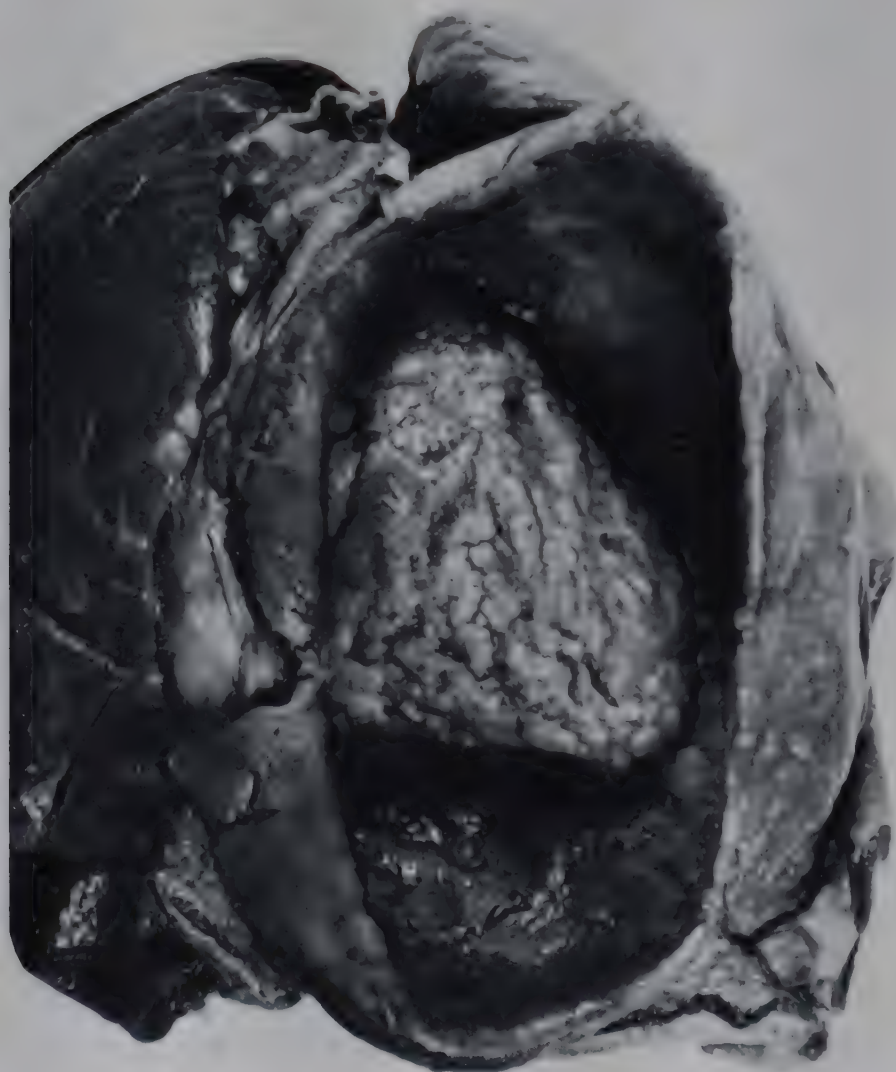


Fig. 58. Acute serofibrinous pericarditis.

spicuous may be called “serofibrinous” or “fibrinoserous” (Fig. 58).

Pyogenic Inflammation. The adjective “py- of exudate and dead disintegrating tissue, in-
 filtrated with numerous leukocytes or their
 remains. The most common causes of pyo-

genic, suppurative, or purulent inflammation are the pyogenic bacteria; that is, staphylococci, streptococci, gonococci, and meningococci. Many other bacteria and chemicals, such as turpentine and croton oil, may under proper conditions provoke a similar reaction.

In the potential or actual cavities of the body such as the pleura, peritoneum, pericardium, subdural space, subarachnoidal space, and the lumens of the hollow viscera, the pus is present in the space, and the term "purulent inflammation" is to be preferred. In solid tissue the disintegration of cells forms

tissue there are hyperemia, edema, cloudy swelling of the fixed tissue cells, and infiltration with polymorphonuclear leukocytes. At the junction of the living and dead tissue there is frequently a zone of inspissated tissue and pus, recognizable both grossly and microscopically, and designated as a "pyogenic membrane."

One of the most constant constituents of purulent exudates is the polymorphonuclear leukocyte. In a later section of this chapter (p. 108) evidence will be presented to show that the intracellular enzymes of the leuko-

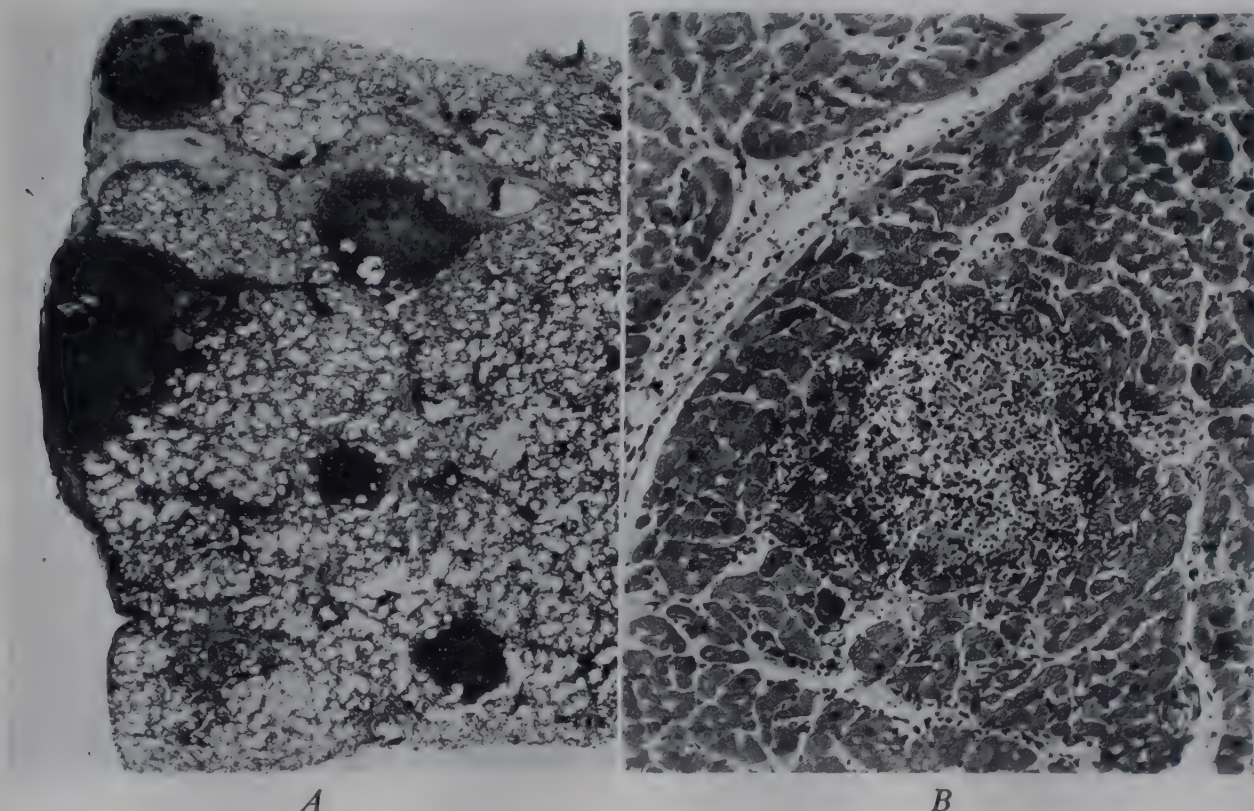


Fig. 59. *A*, Multiple abscesses of the lung. *B*, Abscess of the myocardium.

a roughly spherical cavity filled with pus, and the lesion is designated as an "abscess." A pyogenic inflammation which spreads through the tissues along fascial planes or other natural barriers is referred to as a "phlegmon" or a "phlegmonous inflammation."

The anatomic picture in all is the same: within the preformed or formed cavity there is a thin or thick, yellow or yellowish gray, cloudy or opaque fluid. The color and consistency of the pus vary with the cause. The odor of the pus is usually not offensive, but in infections with *Escherichia coli* and in secondary infections with gas-forming bacilli the odor may be prominent and characteristic. Microscopic examination of the fluid in smears or in sections shows numerous leukocytes and a large amount of amorphous debris and cellular fragments. In the nearest living

cytes are largely responsible for the disintegration of tissue and the formation of pus. However, there are inflammations characterized by the presence of many leukocytes which do not go on to suppuration, such as lobar pneumonia. These should be called "leukocytic inflammations" and not "purulent inflammations."

Hemorrhagic Inflammation. A hemorrhagic inflammation is one in which red blood cells are a prominent component of the exudate. The other constituents vary, and it is customary to use the adjectival synonym "sanguineous," and thus describe "serosanguineous," "sanguinopurulent," and other types of hemorrhagic inflammation. The factors which determine the number of red blood cells in the exudate are many. Some bacteria, notably the anthrax bacillus, characteristically and

regularly provoke a hemorrhagic inflammation. Other bacteria and some viruses may in some instances call forth a hemorrhagic exudate. On serous surfaces many agents evoke an exudate rich in red cells, notably in tuberculous pericarditis and in inflammations resulting from invasion by tumors. In children and in those with some basic disease tending to capillary fragility or hemorrhage, inflammations are often hemorrhagic.

Necrotizing Inflammation. In addition to the death of tissue in pyogenic inflammation, other causal agents induce ischemic or coagulation necrosis of tissue, without the formation of pus. In the intestine some bacteria and chemical substances such as mercuric chloride cause a necrosis of the superficial layers of the mucosa, which then appears as a dull, opaque, bile-stained, friable membrane over a hyperemic, edematous wall. In the appendix, necrosis of a part of the wall leads to perforation, and many use the term "gangrenous inflammation" for this condition.

On the other hand there are certain microorganisms, notably the gas-forming clostridia and the spirochete and fusiform bacilli of Vincent, which characteristically produce necrotizing inflammation.

Inflammation Associated with Infiltration of Eosinophilic and Basophilic Leukocytes. In pyogenic inflammations the causal agent is positively chemotactic for the neutrophilic type of myeloid cell. There are a few disease-producing agents which produce an inflammation and bring into the tissues either the eosinophilic or the basophilic variety of leukocyte. Many of the metazoan parasites, but not all, are positively chemotactic for eosinophils. In the intestinal mucosa of a person infested with hookworms, there are many eosinophils. In infestations with *Trichinella* there are eosinophils about the worm in the muscle and a relative eosinophilia in the blood. An example of a disease characterized by the accumulation of mast cells is urticaria pigmentosa.

Hypersensitive Inflammation. The better-known diseases related to the hypersensitive state are asthma, hay fever, and serum sickness. In all of these the exudate in the local inflammation is rich in eosinophilic leukocytes, and there is frequently a relative eosinophilia in the blood. Because some hypersensitive inflammations show tissue eosinophilia,

it does not, however, follow that all inflammations with tissue or blood eosinophilia have something to do with hypersensitivity. Precise and controlled investigations are needed before any general conclusions concerning the relation of allergy to eosinophilia can be drawn. Probably of greater significance in establishing an inflammation of the hypersensitive type is the presence of fibrinoid in the lesion.

Inflammation Associated with Infiltration of Lymphocytes, Mononuclear Cells, and Plasma Cells. Some bacteria and viruses provoke an inflammation in which the dominant cell in the exudate is a mononuclear cell lymphocyte, plasma cell, or some combination of the three. Thus in typhoid fever almost the only free cell in the lesions is the mononuclear cell. In tuberculosis the dominant cell varies with age of the lesion. Early there are polymorphonuclear leukocytes; later the mononuclear cell and lymphocyte are dominant; and still later the tubercle with giant cells and epithelioid cells is common.

Multinucleated Cells in Inflammation. Under many physiologic and pathologic conditions multinucleated cells appear in tissue. At least eight types have been recognized: the Langhans giant cell of tuberculosis, the foreign body giant cell, the osteoclast, the megakaryocyte, the giant cell of skeletal muscle, the giant cell of nerve tissue, epithelial syncytia, and tumor giant cells (Haythorn). The osteoclasts and megakaryocytes are normal cellular components. The giant cells of muscle, nerve tissue, and epithelium are phenomena of regeneration, and will be discussed in Chapter XI, p. 116, on repair. The true tumor giant cell will be considered in Chapter XIII, p. 127, on tumors.

The Langhans and the foreign body giant cell are the types concerned with inflammation. They are probably fundamentally the same, and differ in structure only because of the environment. The characteristic Langhans giant cells vary greatly in shape, in size, and in number of nuclei. They are round, oval, elliptical, or stellate. They vary from relatively small cells with 2 to 4 nuclei to masses measuring 200 to 300 microns in diameter with over 100 nuclei. The nuclei are round or oval, with sharp outlines and conspicuous nucleoli, and are usually arranged peripherally, with the long axis of the nucleus at right

angles to the cell wall. The foreign body giant cell differs only in the distribution of the nuclei: central, bipolar, or diffuse.

Origin of Giant Cells. Good evidence indicates that the Langhans and the foreign body giant cells are formed from mononuclear cells by fusion or by nuclear division without cytoplasmic division. Which process is operative in any given circumstance probably depends on many factors, particularly on the nature of the foreign body. It is logical to believe

sions called forth by nonliving particulate matter are designated as "foreign body reaction." The more common agents are relatively insoluble in organic and inorganic solvents. Thus if talcum powder (magnesium silicate) is placed in the tissue or in a serous cavity, small nodules composed of fibrous tissue and giant cells develop (Fig. 60). A similar reaction is seen about older areas of fat necrosis about crystals or droplets of lipids (Fig. 25B, p. 44), about indigestible frag-

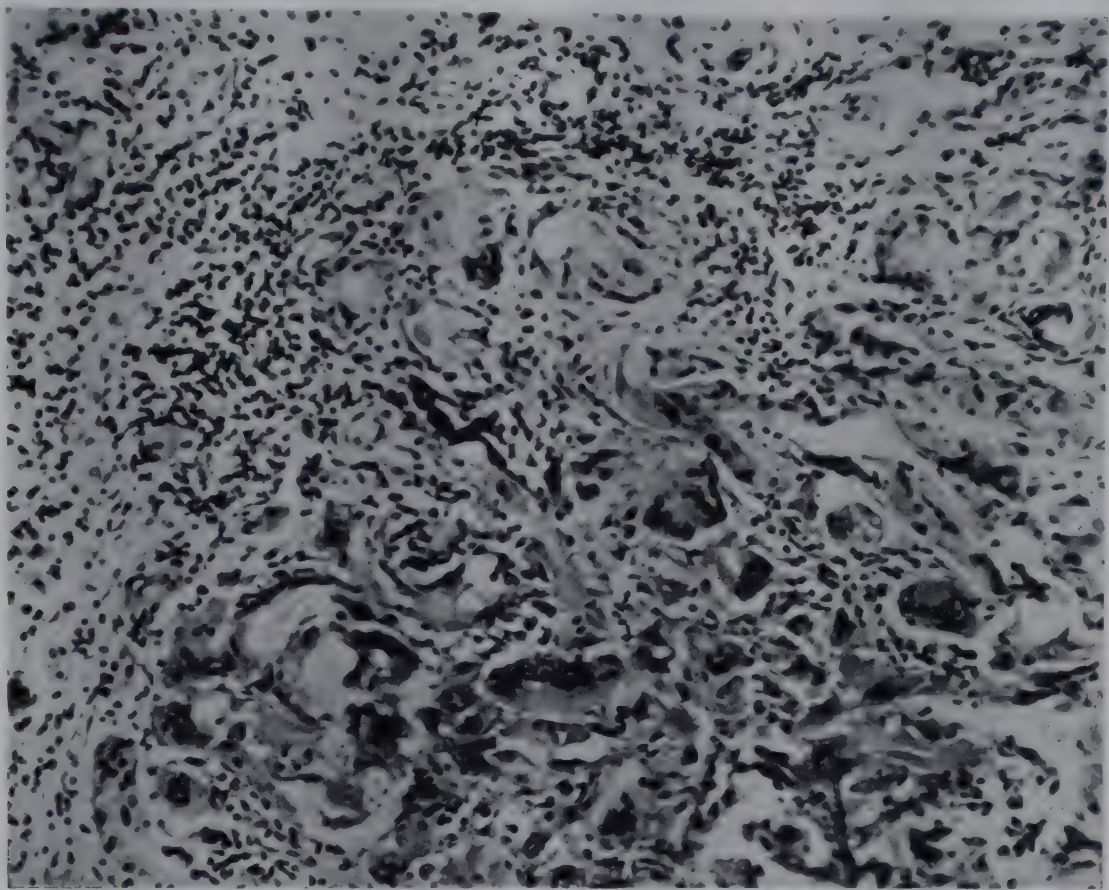


Fig. 60. Foreign body giant cells about crystals of talcum powder.

that as several cells approach an insoluble particle, the surface tensions of adjacent cells become equal and the cytoplasm of all fuses.

Infectious Granulomas. In a number of infectious diseases small or large focal inflammatory lesions form in the tissues. These are known collectively as the infectious granulomas. Notably they are found in tuberculosis and syphilis, and in mycotic, protozoal, and metazoal diseases. The structure of the granuloma varies widely both in those caused by the same agent and in those caused by different agents. In most, at some stage multinucleated cells are present, and it is upon the structure, position, and number of giant cells, together with other observations, that the histopathologist bases a differential diagnosis.

Foreign Body Reaction. Similar focal le-

ments of cellulose, particles of carbon, glass, and other foreign material, and about unabsorbable suture material such as linen and silk in wounds.

Fate of Giant Cells. Giant cells about foreign material may be present many years after it is introduced into the tissue. Although they may not be the original cells, this observation does indicate permanency of structure. In resolution, giant cells either dissolve as a whole, or break up into component single cells.

Subacute and Chronic Inflammation. In all the types of inflammation discussed so far the changes are acute. As the acute inflammation subsides and repair begins, there is proliferation of fixed tissue cells and a transition from a dominant leukocytic exudate to one com-

posed of mononuclear cells and lymphocytes—the resolution and repair in an acute inflammation. Some agents which incite inflammation are relatively inactive and produce only a progressive type of response with pro-

exacerbations of the acute reaction. These two are known respectively as “subacute” and “chronic” inflammation.

In general *subacute inflammations* are characterized by active proliferation of cells, slight

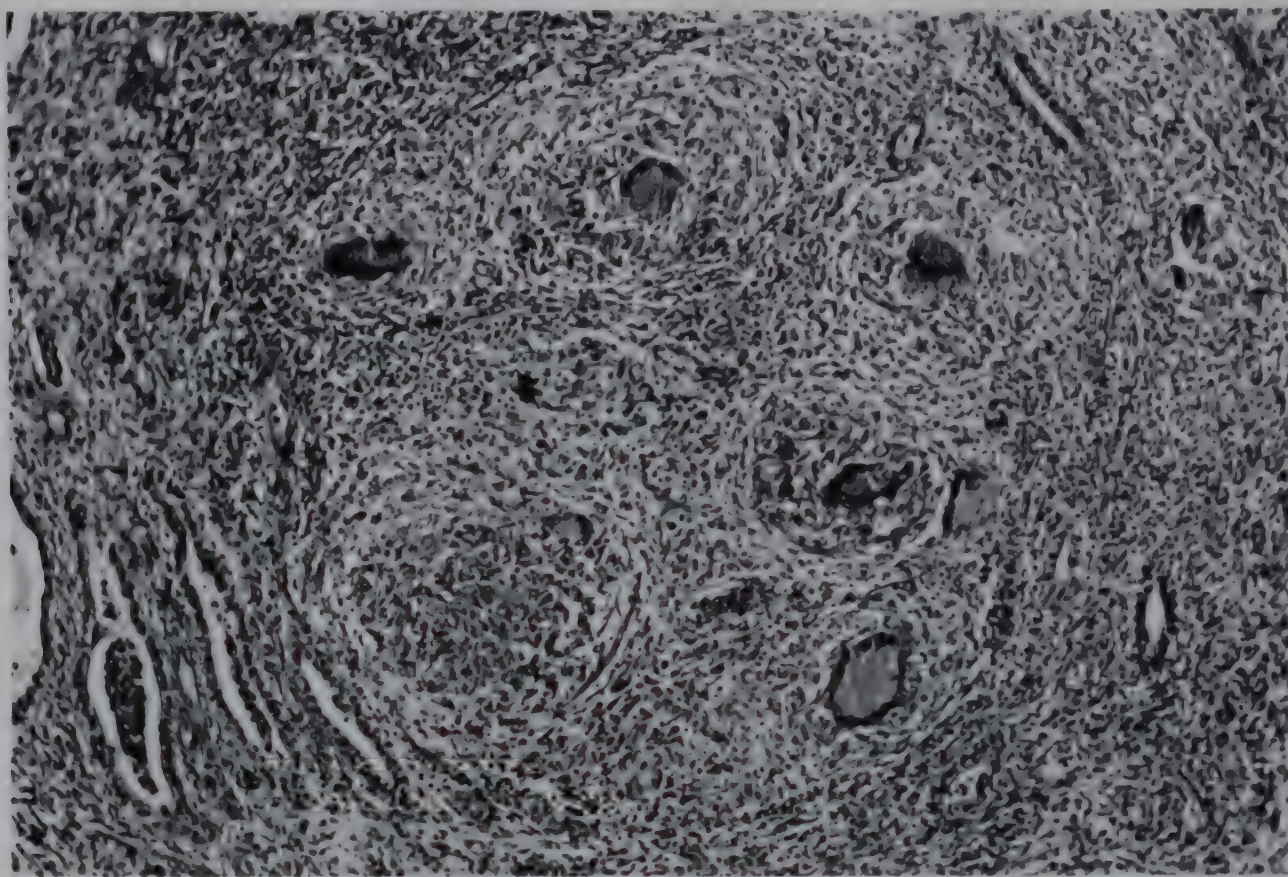


Fig. 61. Conglomerate tubercle in kidney.

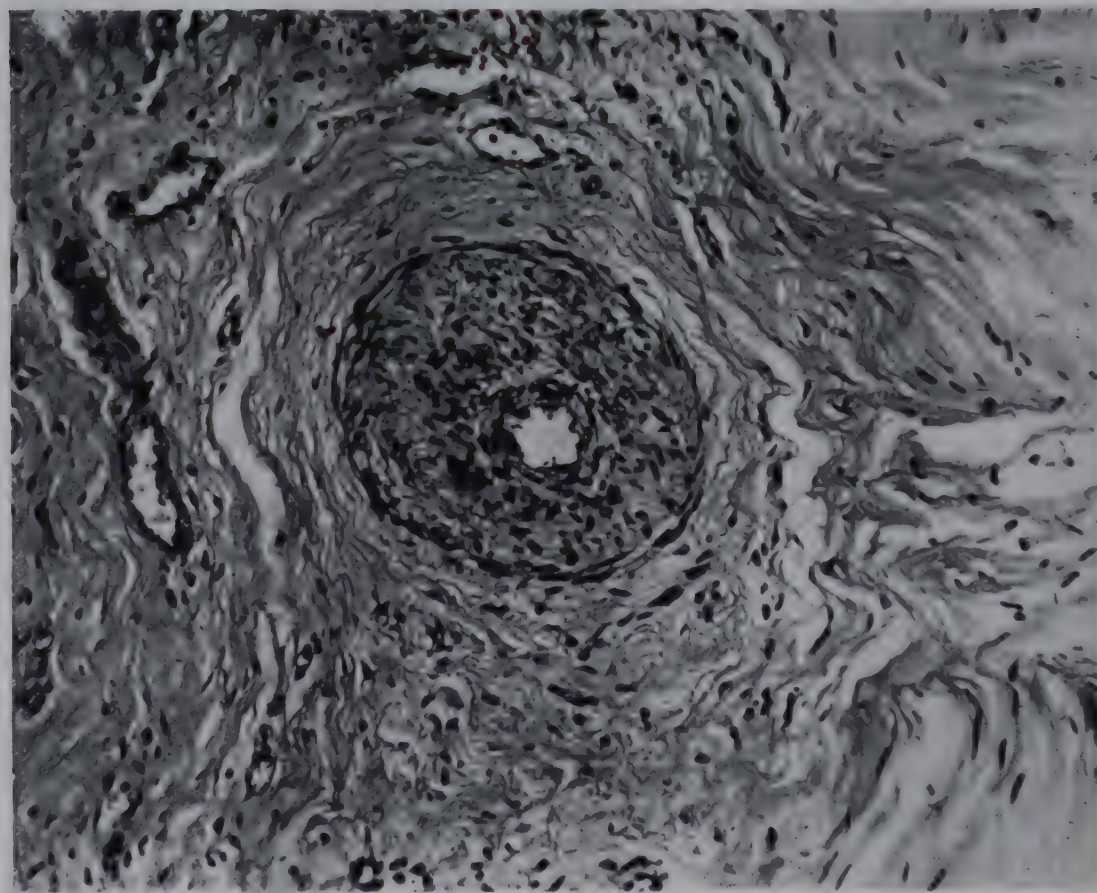


Fig. 62. Fibrosis and proliferative endarteritis in chronic inflammation of the pleura.

liferation of fixed cells and usually little exudation; others produce first an acute reaction and then continue over a period of months or years to call forth a proliferative or productive type of response with or without periodic

edema and hyperemia, and infiltration with lymphocytes, mononuclear cells, plasma cells, and a few polymorphonuclear leukocytes. *Chronic inflammations* involve less active proliferation and greater deposition of collagen

by the fibroblasts, inconspicuous hyperemia and edema, and only slight infiltration with lymphocytes, mononuclear cells, and plasma cells.

Organizing Inflammation. In an inflammatory process not involving destruction of fixed tissue the exudate ordinarily undergoes resolution, and the preexisting structure is restored. In some inflammations of this type, particularly pneumonia, there may be defective resolution and the exudate may be invaded by capillaries and fibroblasts and be organized (Fig. 63). In many inflammations of

diagnosed as chronic inflammation, since the causal agent is no longer present and all possible repair has been accomplished.

Alterative Inflammation. The degenerative changes described in Chapters II to IX represent an entirely different type of response, and it is customary to exclude them from the category of inflammation. However, for those who wish to combine all reactions under the one term "inflammation," the designation "alterative inflammation" may be used synonymously with "degeneration" and "disturbances in the metabolism of cells."

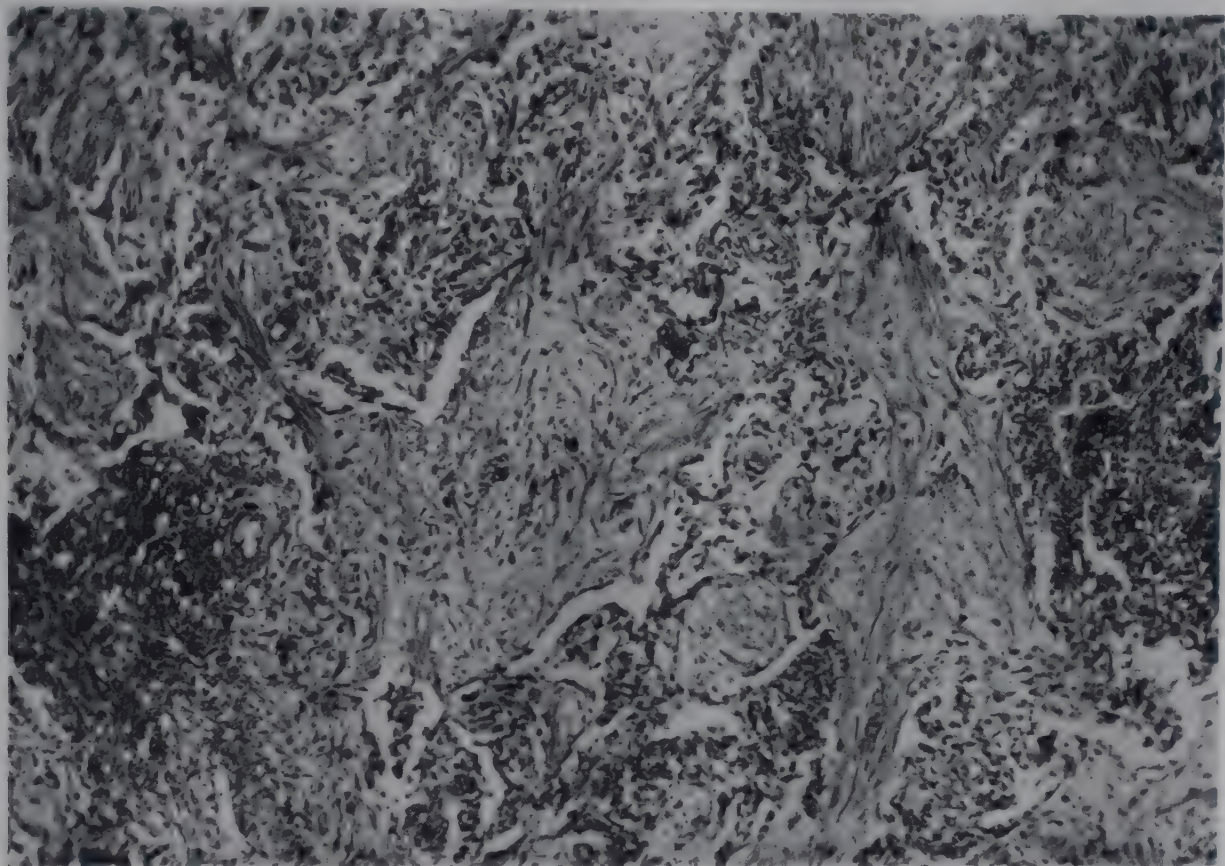


Fig. 63. Organizing pneumonia.

serous membranes the fibrin on the surface is organized. The result is a mass of fibrous tissue in the form either of a plaque on the surface, or of an adhesion between two adjacent surfaces.

Distinction from Similar Lesions. In many organs, notably the heart and kidneys, gradual restriction of blood supply leads to fibrosis and slight infiltration with lymphocytes. To call this lesion in the heart "chronic interstitial myocarditis," is to confuse two causal entities. In the case of the kidney the distinction has been clearly recognized. A chronic inflammation is chronic glomerulonephritis, and fibrosis incident to vascular disease is nephrosclerosis.

For similar reasons the scar in healed inflammation, that is a cicatrix, should not be

Relation of Chemical Structure of the Causal Agent to the Type of Reaction. If the inflammatory reaction is provoked by chemical products elaborated by or in bacteria, the specific nature of each of the inflammatory processes must depend on the nature of the products. By chemical extraction of the lipids, proteins, and carbohydrates of the tubercle bacillus it has been shown that the infiltration with polymorphonuclear leukocytes is caused by the protein and carbohydrate, and that the characteristic tubercle forms in response to a single acid, phthioic acid, contained in the phospholipid of the bacillus. Similar investigations with other bacteria are needed (Sabin).

Spreading Factor. An example of the possible interplay between chemical composition

of tissue and the causal agent is the spreading factor. Duran-Reynals first showed that an injection of an aqueous extract of testis prepares the subcutaneous tissues so that the vaccine virus spreads more rapidly and extensively than in unprepared tissues. This spreading factor in testis is probably hyaluronidase, and it acts by hydrolyzing the hyaluronic acid in the interstitial tissue. Many species of streptococci are rich in hyaluronidase, and this may explain in part the tendency to cellulitis with this organism.

The Physics and Chemistry of the Inflammatory Process

It is convenient at the present time to divide the phenomena of inflammation into two parts, the physics and chemistry of the inflammatory process and the biology of the inflammatory process. In the former are included the changes in the blood vessels, the alterations in capillary permeability, and the migration of cells. The latter comprehends the phagocytic activity of the cells and the functional role of the exuded fluid.

Vascular Reaction. The two components of the vascular reaction in inflammation—dilatation of vessels and slowing of the blood flow—are closely related, but their causes are sufficiently distinct to warrant separate discussion.

Dilatation of the Vessels. Under physiologic conditions the size of the blood vessels in a part is controlled by two sets of nerves, vasodilators and vasoconstrictors. Division of the sympathetic nerve to the rabbit's ear results in vasodilatation. If the ear is then placed in water at 50° C. to incite inflammation, the effect of the injury becomes apparent more rapidly, and the degree of inflammation is greater than in a normal ear. On the other hand, division of the auricular nerve to the ear causes vasoconstriction. Under these conditions a similar thermal injury provokes an inflammation which develops more slowly than under normal conditions. It is thus apparent that an interruption of central nervous control modifies the rapidity of development and the intensity of the inflammatory process, but does not modify it qualitatively. The logical inference is that the vascular reaction is a local process, mediated through axon reflexes, or a direct effect of some chemical

substance on the contractile elements of the walls of the vessels.

Most observations point to the conclusion that the early transient vasoconstriction is caused by nervous stimulation, and that the subsequent, enduring vasodilatation is the result of the direct action of a chemical substance on the vascular wall.

INDIRECT EFFECT OF THE NERVOUS SYSTEM IN INFLAMMATION. Although no direct evidence can be secured to prove that the central nervous system is basically responsible for the vascular reaction in inflammation, there are many indications that it has an indirect influence. Loss of the sensory or motor innervation of a part renders that part more susceptible to injury because of inability to recognize pain or to avoid injury. Additional evidence that inflammation is mediated through the central nervous system is furnished by a number of diseases of the skin in which lesions appear along the course of nerves and are frequently symmetrical on the trunk or on the paired extremities.

The possible relation of hysteria and hypnosis to the localization of inflammation is a moot question. The attempted explanation of the stigmata offers a stimulating field for the psychiatrist and the pathologist (Krumbhaar).

Slowing of the Stream. The rapidity of flow in the early stages is undoubtedly the result of dilatation of the arteries and arterioles without equal dilatation of the capillaries. The blood pressure is thus brought into smaller vessels, and the blood is pushed on at an increased rate. With the establishment of capillary dilatation the blood flow in the part slows and may even come to a standstill. Many factors are responsible for the capillary stasis: dilatation of capillaries and creation of a greater volume, increase in the viscosity of the blood, swelling of the endothelial cells, and possible alteration in the interfacial tension between the endothelium and the blood.

The *increase in the viscosity of the blood* is in turn related to a number of factors: hemoconcentration resulting from the exudation of fluid, swelling of the red blood cells because of accumulation of the acidic products of metabolism, alterations in the viscosity of the hydrophilic plasma proteins, and compression of the venules by the exudate in

the tissues and blockage of the flow of blood from the part.

The swelling of the endothelial cells decreases the caliber of the lumens of the capillaries and is probably caused by the imbibition of water incident to the accumulation of acids in the cells. The assumed *change in the interfacial tension* of the endothelium and blood and an increased stickiness of the vascular wall are difficult to define objectively.

Cellular Migration. Chemotropism. One of the most characteristic features of inflammation is the presence within the tissue of various types of wandering cells, leukocytes,

there is negative chemotropism for the polymorphonuclear leukocyte.

Factors Influencing Locomotion and Degree of Chemotropism. The studies of McCutcheon and his associates during the past twenty years have thrown considerable light on the process of chemotropism as it applies to mammalian physiology. They have shown that leukocytes are attracted positively by most bacteria (McCutcheon and Dixon); but in moving toward a bacterium they do not travel more rapidly than they do when moving at random (Dixon and McCutcheon). At least in experimental animals, immunization

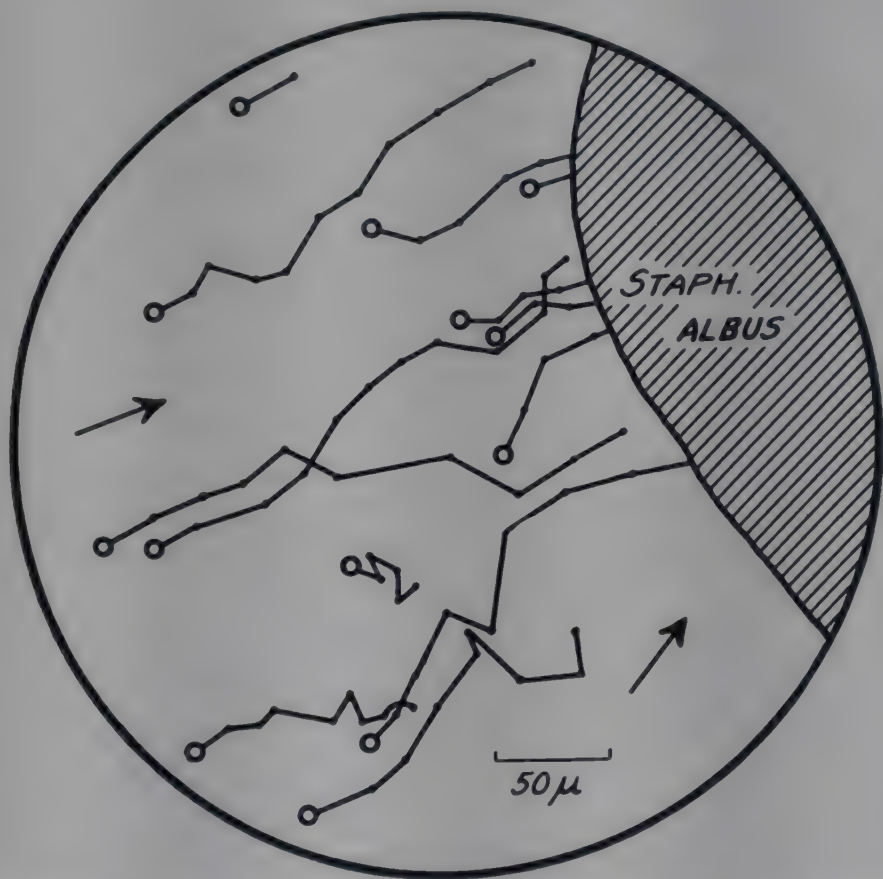


Fig. 64. Diagram of the track taken by leukocytes under the influence of positive chemotropism. (McCutcheon, Coman, and Dixon: Arch. Path., Vol. 27.)

lymphocytes, plasma cells, mononuclear cells, and eosinophilic leukocytes. In normal tissue there are only a few of these cells within the interstitial spaces. It is evident that they must be mobilized from other points during the inflammatory reaction. The force which pulls these cells into the area of inflammation is known as "chemotropism." In terms of general biology, chemotropism may be either positive or negative; in other words, cells may be attracted or repelled by a given substance. In inflammation we are concerned largely with positive chemotropism, although there are some inflammations, such as that in typhoid fever, in which it would appear that

has no influence on the velocity of locomotion, or on the degree of positive chemotropism (Coman, McCutcheon, and De Camp). On this basis the nonimmune organism should mobilize leukocytes through vascular walls in an area of inflammation as well as the immune organism. Leukocytes taken from a patient with an acute infectious disease show a decreased rate of locomotion and a smaller degree of positive chemotropism (Mallery and McCutcheon). On the other hand the increased temperature during an acute infectious disease has a material influence on the velocity of motion of the leukocyte: a moderate increase in the temperature promotes the

activity of leukocytes, but an excessive increase of temperature decreases the activity of leukocytes. In broad terms, then, speaking only of chemotropism, a moderate fever in association with an infection is beneficial, and a temperature above 41° or 42° C. is detrimental to the defensive mechanisms. It is of interest that the sulfonamide drugs have no influence on chemotropism, and their action must be attributed to other influences. In strong concentrations they are actually toxic to leukocytes (Coman).

In contrast with the leukocyte, the lymphocyte shows little evidence of positive chemotropism for any of the substances which have been tested (Dixon and McCutcheon).

The Mechanism of Chemotropism. There are two possible explanations for chemotropism: that it is an electrical phenomenon, and that it results from differences in surface tension. There is no conclusive evidence for or against either theory, although the electrical theory has more to favor it. In a cataphoretic chamber the leukocytes exhibit a negative charge and migrate to the positive pole at the rate of about 0.51 micron per minute. In the circulating blood a certain force would be necessary to hold a leukocyte on the wall of the capillary, and under normal conditions this force equals the energy of about 7×10^{-5} dynes. With an assumed potential drop of 0.1 volt per centimeter between the blood and an area of inflammation, there are sufficient electrical forces to cause a leukocyte to travel a distance of 100 microns in thirty-four minutes. Expressed in another way, if the wall of the capillary is 0.1 micron thick, it would require an electrical force of from 0.1 to 1 millivolt to force a leukocyte through the capillary wall. All of these assumed conditions and results are consistent with observations, and it follows that chemotropism may well be the expression of an electrical phenomenon (Abramson). How a difference in electrical potentials between normal and injured tissue is established is not understood.

Increased Capillary Permeability. Passage of fluid from the vessels into the tissues in inflammation follows the general principles detailed in the section on edema (Landis). The simple mechanical forces to drive fluid through the semipermeable endothelium may be expressed as:

$$F = (C.P. - T.P.) - (O.P.P. - O.P.T.)$$

when C.P. is capillary pressure, T.P. is the pressure of the tissue fluids, O.P.P. is the osmotic pressure of the plasma proteins, and O.P.T. is the osmotic pressure of the tissue fluids.

Increase in Capillary Pressure. With the onset of inflammation there is an increase in capillary pressure so that the available force to push fluid into the tissues is increased. In the web of a frog's foot this elevation after application of a crystal of silver nitrate may be as much as 16.5 to 19.5 cm. of water within the first twenty minutes.

Increase in Cellular Permeability. A second factor is the damage to the semipermeable membrane of endothelium, allowing larger molecules to pass through. If a dye such as trypan blue is injected intravenously and a focal region of inflammation observed, the dye will pass into the inflamed tissues diffusely, proving that the increase in permeability is not through the formation of small stomas between cells, but through an increase in the permeability of the entire cell. The plasma proteins similarly pass through more easily. Even particulate matter such as graphite, which normally fails to pass through the endothelium, can be seen to go through the capillary wall into the tissues.

Alterations in Forces. As fluid starts to leave the vessels there is a constant shift in the four variables of the formula. If a fluid poorer in protein than the plasma is exuded and the vascular reaction has reached the stage of relative stasis, there is an intravascular concentration of plasma proteins and a corresponding increase of the osmotic pressure which will hold fluid inside the vessels. Conversely, if the exudate is rich in protein, the osmotic pressure of the tissue fluids is increased, and the force is in reverse. As the fluid accumulates in the tissues, the venous side of the circulation, where the vascular pressure is the lowest, is compressed. The net result from occlusion of the veins is heightening of the arteriolar pressure and an increase of the forces which drive fluid out of the vessels. Further, the increase of extravascular tension operates against capillary pressure, and passage of fluid into the tissues diminishes (Rigdon).

The Biology of the Inflammatory Process

CELLS OF THE EXUDATE

From the standpoint of function, the inflammatory process is directed toward minimizing the effect of the injurious agent on the tissues. This function is fulfilled in two general ways: (1) mobilization of phagocytes, and (2) exudation of fluid into the tissues.

Phagocytosis. After the classic studies of Metchnikoff, it was believed for some time that the most important part of the inflammatory reaction was the engulfing of the offending bacteria by what were termed the "microphages" and the "macrophages," now known as "polymorphonuclear leukocytes" and "mononuclear cells." Shortly thereafter, Wright enunciated the general principles of the action of opsonins, and for many years a controversy raged concerning the relative importance of the phagocytes and opsonins in the destruction of bacteria. It gradually became evident that both are important.

Determination of the Opsonophagocytic Index. If leukocytes, serum, and bacteria are mixed and incubated, a certain number of bacteria are phagocytized by the leukocytes. The number of cells containing bacteria and the average number of bacteria within each cell are an index of the activity of the leukocytes of a given animal organism and of the promotion of phagocytosis by the opsonins in the blood serum. By variation of either factor it can be shown that immature leukocytes are not so active as mature leukocytes and that the opsonic activity of the blood of children is not so great as that of adults (Hektoen). In fact during the first month of life there is a precipitous fall in the opsonic index, which does not again reach a normal value until the second year of life (Tunnicliff). This fact may explain the increased susceptibility of infants to certain infectious diseases. Immunization of an animal organism increases the opsonic index of that organism. This phenomenon is apparently in part nonspecific, since the mononuclear cells of tuberculous guinea pigs exhibit greater phagocytic capacity for carbon particles and for staphylococci than do the mononuclear cells from normal animals (Lurie).

Physiochemical Explanation of Phagocytosis. There are two possible explanations of

the phenomenon of phagocytosis: (1) that it depends upon differences in electrical potential, and (2) that it is a phenomenon of the spreading of proteins over surfaces. The greater mass of the evidence indicates that the latter theory is correct. When a particle is brought in contact with a phagocyte, there are three interfacial tensions to be considered, as shown in Fig. 65. S_1 is the interfacial tension between the particle and the fluid, S_2 the interfacial tension between the phagocyte and the fluid, and S_{12} the interfacial tension between the phagocyte and the particle. Anything that increases S_1 and decreases S_{12} will

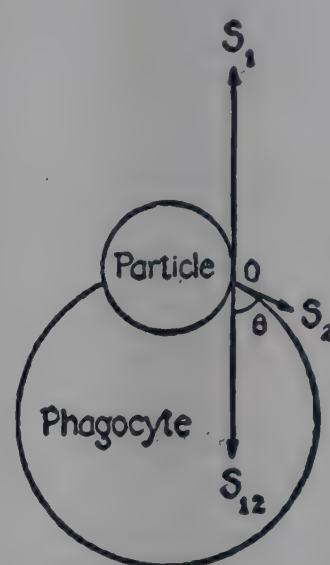


Fig. 65. Diagram of the interfacial tensions effective in phagocytosis. (Mudd: Cold Spring Harbor Symposia on Quantitative Biology.)

promote phagocytosis. Thus whether or not phagocytosis occurs might be expressed by the following two general statements: When S_1 is greater than $S_{12} + S_2$ the phagocyte will surround the particle, and when S_{12} is greater than $S_1 + S_2$ there will be no phagocytosis (Mudd, McCutcheon, and Lucke).

It is probable that the serum proteins, and specifically the opsonins, influence phagocytosis by increasing S_1 and decreasing S_{12} . On fractionation of the proteins the order of their effectivity is: whole serum, euglobin, pseudoglobulin, and albumin.

Fate of Ingested Particles. If the phagocytized particle is a bland substance which has no solubility, such as a particle of carbon dust, there is no effect on either the particle or the phagocyte. If the particle is an organic or inorganic chemical substance which is soluble and toxic, such as silica, the phagocyte is

killed. If the ingested particle is a bacterium, the phagocyte may be killed, the bacterium may be killed, or the two may live in symbiosis. This symbiotic association is of considerable importance in the pathogenesis and treatment of disease. It may explain the chronic progressive nature of some diseases, notably kala-azar and leprosy in which neither the bacterium nor the phagocyte has the ability to destroy the other. An additional point is that bacteria contained within cells are probably protected from the action of humoral antibodies and may survive for long periods of time. This protection from antibodies is a point of major importance in an evaluation of viral diseases, where the parasites are obligate intracellular organisms (Rous and Jones).

Factors Influencing Phagocytosis. Aside from the maturity of the leukocyte, the patient's age, and the immune state, other factors determine the activity of phagocytes. In the range between 5° and 35° C. an increase in temperature of 10° doubles the amount of phagocytosis. After a phagocyte has phagocytized one particle, there is no influence on further phagocytosis until the number of particles within one cell become excessive (Mudd, McCutcheon, and Lucke). General undernutrition and starvation depress the activity of phagocytes, a fact which is correlated with the well known susceptibility of undernourished persons to infectious diseases (Gellhorn and Dunn).

FLUID OF THE EXUDATE

The fluid part of the exudate is useful to the animal organism in two ways: (1) to dilute the injurious agent, and (2) as a vehicle for specific substances such as fibrinogen, enzymes and antienzymes, and antibodies.

Dilution. The role of fluid in dilution of the inciting agent is well illustrated in pleurisy in dogs provoked with turpentine. If 1 cc. of turpentine is injected into the pleural cavity, a serofibrinous inflammation rapidly develops. For the first two or three days there is a gradual increase of fluid and a gradual decrease in the perceptible odor of turpentine. By the third day the fluid averages 100 cc. in amount, and the turpentine has been diluted and absorbed and is no longer present in sufficient concentration to incite inflammation. Hence the fluid is rapidly resorbed into the blood and lymphatics, the fibrin is gradually digested

by enzymes, and the normal structure is restored in two or three weeks. In contrast, the injection of turpentine into the subcutaneous tissue, in which the tension limits the accumulation of fluid, results in a pyogenic inflammation, and the odor of turpentine can be detected for many days (Opie).

Fibrinogen and Mechanical Fixation. Fibrinogen in the exudate rapidly gels to fibrin. The threads of fibrin pervade the tissue spaces, and it is possible that the spread of bacteria is mechanically impeded by this network. Of much importance in blocking dissemination of the bacteria are the thrombi of fibrin in the lymphatics and venules (Menkin). Since immune bodies exert a greater influence on local fixation in bacterial disease than do mechanical factors, further discussion of this point will be given in the succeeding paragraphs.

Enzymes and Antienzymes. Of importance in an understanding of the mechanism of resolution in inflammation are the enzymes and antienzymes contained in the fluid and cells of the exudate (Opie).

Leukoprotease. Polymorphonuclear leukocytes contain an enzyme capable of digesting proteins and forming peptones and polypeptides, both of which are present in exudate. So long as the cell is alive these enzymes are contained within the cytoplasm, but with death of the cell the enzymes are liberated into the surrounding fluid.

Antileukoprotease. If there were no mechanisms to inhibit the action of leukoprotease, all inflammatory processes would involve an excessive destruction of tissue. The reason that this does not occur is that the plasma contains an antienzyme. Thus, if one mixes leukoprotease with plasma there is no digestion of proteins. The most convenient method for the preparation of leukoprotease is to dry the leukocytes by chemical or physical methods, and resuspend the powder in normal saline. This suspension or solution, when added to gelatin or to coagulated serum, within a few hours brings about digestion of both, if the hydrogen ion concentration is slightly alkaline, that is, between 7.6 and 8. If normal serum is added to the suspension, there is no digestion.

Lymphoprotease. In contrast with the enzymatic activity of the polymorphonuclear leukocyte, preparations of mononuclear cells, most conveniently made from a suspension of

lymphoid tissue, contain an enzyme which is active on the acid side of the normal pH of the blood, that is, between 7 and 7.4.

Erepsin. In pus there are not only polypeptides and peptones, but also free amino acids, and it can be easily demonstrated that the polymorphonuclear leukocyte contains, in addition to leukoprotease, an enzyme similar to erepsin which will break the polypeptides to free amino acids.

Serum Protease. By proper technique the antiprotease of the serum can be separated, and the resulting solution exhibits proteolytic activity; it must therefore be assumed that serum contains a protease similar to but not identical with that in the polymorphonuclear leukocyte.

Role of Enzymes and Antienzymes in Inflammation. If an exudate is poured into the pleural cavity in response to some irritating agent, there is a large quantity of fluid and relatively only a few cells. This inflammatory exudate contains a great excess of antienzyme derived from the serum, and only a small amount of active leukoprotease derived from the leukocytes. Any leukoprotease liberated by the death of leukocytes is immediately neutralized by the antienzyme, and there is a minimal amount of digestion of the exudate and of the surrounding tissues. On the other hand in the subcutaneous tissues there is a distinct limitation on the amount of fluid which can pass into the tissue, and there results a large excess of cells and a minimal amount of fluid. The death of the leukocytes liberates a large amount of enzyme which is not completely neutralized by the antienzyme of the fluid. Necrosis and abscess formation result.

So far as is known, these enzymes exert no effect on living bacteria, but they will digest dead bacteria in the same way they will digest dead and injured cells. Thus the enzymes are concerned not with the immediate defense against the invading injurious agent, but with the digestion of the dead tissue and the eventual resolution of the inflammation.

Metabolism at the Local Site of Inflammation. As inflammation proceeds there is an initial alteration of hydrogen ion concentration to the alkaline side, followed within a few days by a trend toward the acid side of neutrality. This change in pH is correlated in general with the character of the cell in the exudate (Menkin). Thus, early there are poly-

morphonuclear leukocytes bathed in a fluid slightly alkaline and therefore optimal for the action of leukoprotease. During the period of resorption after the height of the inflammation, the dominant cell is the mononuclear cell, bathed in a fluid slightly on the acid side of normality and hence optimal for the action of lymphoprotease.

The increase of hydrogen ion concentration is referable to a depletion of the alkali reserve and an increase in the rate of glycolysis. The latter is reflected in an enhancement in the consumption of oxygen and an elevated metabolic rate. It is possible that some of the differences in the local manifestations of inflammation caused by various agents may be ascribed to different disturbances in the intermediary carbohydrate metabolism of the affected tissue.

ANTIBODIES IN THE FLUID OF THE EXUDATE

There are many ideas concerning the nature of immunity and of hypersensitivity, and of the relation between the two. In the following paragraphs an attempt will be made to demonstrate the influence of the immune and hypersensitive states on inflammation, without entering into the controversy on the fundamental nature of the two phenomena.

Local Fixation of the Antigen at the Portal of Entry and in the Regional Lymph Nodes.

The Arthus Phenomenon. In 1903 Arthus observed that the repeated injection of an antigen (horse serum) into rabbits provokes an increasing reaction. Thus, following the first injection, the antigen rapidly enters the blood stream and no local reaction results from the injection. However, following the fifth or sixth weekly injection the local site becomes swollen and red, and in many instances there is central necrosis with ulceration. Since that time this reaction has been known as the "Arthus phenomenon."

In 1924 Opie demonstrated that the intensity of the Arthus phenomenon closely parallels the amount of titrable precipitin in the circulating blood. He further showed that with simple antigens, such as crystalline egg albumin, the injection of a large amount of antigen provokes the Arthus phenomenon, and that previously demonstrable precipitins disappear completely from the blood. From these studies Opie concluded that the inflammatory reaction, consisting of edema, hyperemia, in-

filtration with polymorphonuclear leukocytes, and necrosis, is the result of the union in the tissues of an antigen and specific antibody—precipitin. He further looked upon this process as a method of fixation, since the result is the holding of the injected antigen at the portal of entry. Up until this time, the fact that a specific inflammatory reaction occurs with growing intensity in a hypersensitive or immune animal was a paradox. Immunity supposedly represents resistance, yet under the

Local Fixation in Inflammation. Opie's work stimulated many other investigators, and there is now abundant evidence that fixation applies not only to purely immunologic processes, but also to many simple chemical substances. Menkin has shown that trypan blue introduced into an area of inflammation does not leave that area. Menkin believes that thrombosis of the lymphatics around the area of inflammation is the principal mechanism by which fixation is accomplished. It is apparent

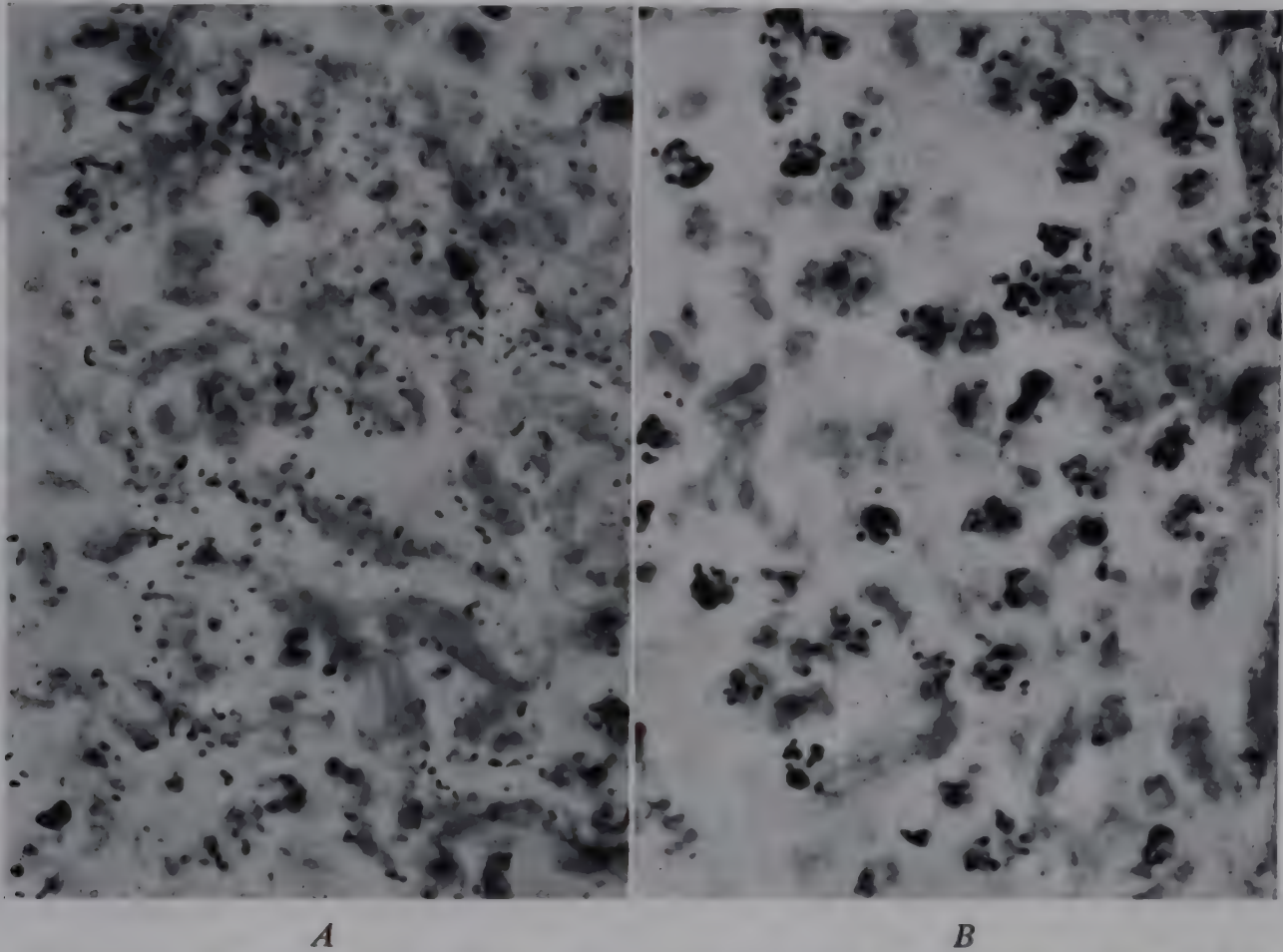


Fig. 66. *A*, Uniform dispersion of bacteria in inflammation of a nonimmune animal. *B*, Agglutination and phagocytosis of bacteria in inflammation of an immune animal. (Photographs by courtesy of Dr. Paul Cannon.)

conditions of the Arthus phenomenon, immunity is correlated with a more severe reaction to the specific antigen.

"The local fixation of antigen removes this contradiction," Opie wrote, "for at the expense of a heightened inflammatory reaction, resulting perhaps in local death of tissue, that is, the Arthus phenomenon, the action of the injurious agent is limited to its portal of entry, and the organism as a whole is protected. It is unnecessary to assume that the tissues of the immunized animal are more sensitive than those of the normal animal to the action of the antigen, for in both the normal and the immune animal the same inflammatory reaction occurs when antigen and antibody meet within the tissues" (see also Cannon and Marshall).

from the work of Opie that this is not the only mechanism, since actual precipitation of soluble antigens is a sufficient explanation. In addition, observations of Cannon and of Rich show that bacteria are clumped in an area of inflammation, and thus cannot move as freely through the tissue spaces (Fig. 66). Cannon's observation that the bacteria in a local area of inflammation are swollen and acquire a stickiness, so that they adhere to the phagocytes, is another factor which contributes to fixation. From a study of chemical substances of various natures Miller concluded that inflammation inhibits the absorption of undiffusible proteins, carbohydrates, and dyes, but that it tends to accelerate the absorption of diffusible carbohydrates and dyes.

The Spread of Bacteria in Tissues. The studies of Angevine clearly extend these biologic principles to living bacteria, as is shown in Table 1. Thus, with avirulent streptococci producing skin sensitivity, hypersensitive in-

Invasion of the Blood by Bacteria. Despite the mechanisms outlined in the foregoing for fixing bacteria at the local portal of entry, a few may escape into the blood. In some diseases such as malaria the parasite does not

TABLE 1. FATE OF VIRULENT OR AVIRULENT STREPTOCOCCI INJECTED INTO NORMAL, SENSITIZED, OR IMMUNIZED RABBITS

	Normal Rabbits			Sensitized or Immunized Rabbits		
	No. Rabbits	With Cocci		No. Rabbits	With Cocci	
		No.	Per Cent		No.	Per Cent
<i>Avirulent:</i>						
Inguinal node	27	17	62.9*	24	7	29.1†
Iliac	5	2	40.0	5	0	0.0
Blood	16	1	6.2	16	0	0.0
Spleen	20	6	30.0	13	0	0.0
Liver	12	0	0.0	12	0	0.0
						50.0
<i>Virulent:</i>						
Inguinal	12	11	91.6	12	6	
Iliac	10	5	50.0	10	0	0.0
Blood	12	2	16.6	12	0	0.0
Spleen	12	4	33.3	12	0	0.0

* 46 bacterial colonies per node.
† 4 bacterial colonies per node.

flammation may be demonstrated; while with virulent streptococci producing immunity, immune inflammation may be demonstrated. It is entirely possible that these two phenomena represent only different phases of the same process. For example, if the vaccination with

localize at the portal of entry, but regularly invades the blood stream in large numbers.

The Fate of Bacteria in the Blood. Lurie injected living virulent tubercle bacilli intravenously into rabbits, some of which had received previous injections of relatively avir-

TABLE 2. FATE OF TUBERCLE BACILLI IN ORGANS OF REINFECTED RABBITS

Interval	Lung		Liver		Spleen		Kidney		Bone Marrow	
	1st Infection	Reinfection	1st Infection	Reinfection	1st Infection	Reinfection	1st Infection	Reinfection	1st Infection	Reinfection
1 day.....	—	20	3	11	16	12	0	405	2	3
1 week.....	6	70	—	31	537	8	6	0	0	0
4 weeks.....	1080	10	—	0	466	0	297	0	170	11
2 months.....	3100	260	2	0	130	0	620	0	1300	0

the avirulent streptococci had been continued until immunity was produced and skin sensitivity lost, the results in the two series of experiments might have been identical. This local fixation of relatively virulent and avirulent bacteria can also be demonstrated with the tubercle bacillus (Freund and Angevine).

ulent human tubercle bacilli. After varying periods of time the lungs, liver, spleen, kidney, and bone marrow were removed, and a weighed portion of the organ cultured. It was thus possible to approximate the total number of living bacilli, in a given tissue at any time, as shown in Table 2. The existence of a pre-

vious infection with tuberculosis materially influences the multiplication of the bacteria after intravenous injection. It is apparent then that a rabbit which shows a positive reaction of the skin to tuberculin has some mechanism for disposing of tubercle bacilli which is not possessed by the animal which has a negative skin reaction.

Agglutination in Vivo. The mechanism of this increased ability of the immunized animal organism to dispose of bacteria is illustrated by the experiments of Cannon with staphylococci. Guinea pigs were vaccinated with formalinized staphylococci, and then living bacteria were injected intravenously and the tissues studied histologically. In the immunized animal Cannon reports the bacteria in the spleen and in the liver are not equally distributed through the tissues, but are found in foci (Fig. 66). This clumping of bacteria in the immunized animals is interpreted by Cannon and others as evidence of *in vivo* agglutination. Cannon also observed that the bacteria are swollen and held to the surfaces of the macrophages and endothelial cells. It seems probable that some immune body in the serum of the immunized animal coats the surfaces of the bacteria and promotes adherence to cells with a similar surface structure. Thus, wherever there are cells of the reticulo-endothelial system, bacteria are withdrawn from the blood stream and fixed at that point. If they are not in great numbers, phagocytosis and other processes kill and destroy them. If they are in excessive numbers, they continue to grow and produce abscesses at many points throughout the body.

Mobilization of Macrophages in the Immune Animal. Taliaferro and Cannon, working with malaria, have demonstrated another process by which the immune animal is more capable of disposing of an infectious agent in the blood stream. In monkeys with superinfection they observed a greatly increased number of macrophages in the spleen and, to a less extent, in other organs containing progenitors of this cell. In a monkey with superinfection, as many macrophages may be mobilized within one hour as become available to the animal with a first infection after from one to two weeks. These mobilized macrophages exhibit greater phagocytic activity, and Taliaferro and Cannon conclude that the cellular immunity in malaria depends on two factors,

first, an increased number of macrophages, and second, an increased phagocytic activity of all of the macrophages.

Local Immunity. Taliaferro and Cannon are of the opinion that a general immunity represents only the establishment of a high degree of immunity at certain critical locations in the body, and their work logically leads to a discussion of the phenomena of local immunity and resistance.

Local Resistance. A nonspecific inflammation produced with aleuronat in the pleural cavity or in the peritoneal cavity confers a certain degree of resistance against a subsequent inflammation with streptococci (Gay; Opie). Forty-eight hours after the onset of an inflammation produced with aleuronat, a dog survives an infection of the peritoneal cavity with streptococci, and bacteria do not enter the blood (Opie). Protection against the second inflammation begins when the cytologic picture of the first inflammation is predominantly monocytic (Gay). This nonspecific resistance in the serous cavities has been utilized by surgeons in the protection of the peritoneum during operations on the large intestine.

Local Immunity in the Nasal Mucosa and Local Formation of Antibodies. Walsh and Cannon attempted to demonstrate a similar phenomenon in the nose. They introduced into the nasal cavity of rabbits, and subsequently of man, formalinized vaccines, and studied the histologic appearance of the nasal mucosa, and the titre of antibodies in the nasal mucosa, in the blood, and in other organs. Their results clearly indicate that under these conditions an active immunity of the nasal mucosa can be secured, and that the nasal mucosa contains a higher titre of antibody than any other organ, in many instances approaching the titre in the blood. Histologically, the nasal mucosa of a vaccinated animal shows the first stages of inflammation, hyperemia, and infiltration with an increased number of monocytes, and is therefore more capable of dealing with secondarily introduced bacteria.

Changes in Epithelial Cell Type with Resistance. Francis and Stuart-Harris observed that ferrets which had recovered from influenza were not susceptible to a second inoculation for a period of from six to eight weeks. Histologic study of the nasal mucosa of these animals shows that this resistance is directly

correlated with the appearance of a stratified epithelium in the nose and over the turbinates. After six weeks the epithelium gradually reverts to the normal columnar epithelium, and the animal is again susceptible to influenza.

Nature and Function of Inflammation —Definition

Inflammation is the sum total of the changes in the tissues of the animal organism in response to an injurious agent, including the local reaction and the repair of the injury. If the inflammatory reaction is adequate, it minimizes the effect of the injurious agent, destroys the injurious agent, and restores the part to as near normal structure and function as possible. If it is not adequate, there are extensive destruction of tissue, invasion of the body, and somatic death.

Selected Views. In order that the reader may integrate this concept with the ideas of others, selected definitions or explanations given in other textbooks and monographs are quoted:

“Inflammation is a complicated vascular and cellular response, which follows almost immediately upon the injury, and is adapted, by bringing much blood to the spot and pouring out its elements upon the injured tissue, to prevent the extension of the injury, hold in check the injurious agent, or even to destroy it” (MacCallum).

“Inflammation includes all the phenomena observed from the time of injury to the time of complete repair, thus including a series of reactive processes in the vessels and tissues which follow upon injuries of chemical, physical, or infectious nature, run a more or less regular course, and in favorable cases result in the destruction and removal of the injurious substances and lead to repair and healing” (Karsner).

“Inflammation is the series of changes constituting the local manifestations of the attempt at repair of actual or referred injury to a part” (Adami).

“Inflammation is the local reaction of the body to irritation” (Boyd).

“Inflammation is the process by means of which cells and serum accumulate about an injurious substance and tend to remove or destroy it” (Opie).

“Inflammation . . . consists of a progression

of tissue actions and alterations which in the main serve the useful purpose of protecting the body against agents which tend to injure and destroy it” (Forbus).

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XI

Repair: Healing of Wounds

As the defenses of the body overcome an injurious agent the inflammation subsides, but two processes remain to be carried out: (1) removal of the exuded fluid and cells and dead tissue, and (2) repair of any damage to the fixed tissue. The first of these has been discussed in the preceding chapter under the caption "Fluid of the Exudate" (p. 108). The extent of repair of a defect in the fixed tissue depends on the capacity of cells to proliferate.

Regenerative Capacity of Cells and Tissues

In many injuries and inflammations there is destruction of fixed tissue. The capacity of the body to repair the defect and restore normal structure and function varies with the type of tissue or cell destroyed. In the succeeding paragraphs the ability of each of the more important cellular types to regenerate will be considered.

Regeneration in Lower Animals. Regeneration in the lower animals is frequently unlimited. A part or an extremity is completely replaced and sometimes when an animal such as an earthworm is divided in two, each part becomes a complete animal organism. The same is true in the plant kingdom. However with specialization and the development of more complex species, regeneration becomes limited. In a fully developed adult tree, new limbs may develop, but if a limb is removed there is no regeneration from the stump.

Physiologic Regeneration. There are many tissues in the body which are constantly replaced: the epidermis, the epithelium of the urinary tract, and to some extent the epithelium of the alimentary canal and respiratory tract. In bone there is constant readjustment of the trabeculae to meet the varying strains and stresses of life. In all of these the same

biologic principles are operative as are applicable in the repair of injury.

Epithelium. The epithelium covering the face of the body and lining the hollow viscera and many of the specialized secretory cells derived from epithelium have great capacity for regeneration.

Surface Epithelium. The epidermoid epithelium of the skin and the columnar and transitional cells of the viscera rapidly proliferate and cover a defect. At the edge there is multiplication of the cells of the lower undifferentiated layers, and cells move out into the uncovered surface by ameboid motion. On the cornea the integrity of the epithelium after a minimal injury may be restored in from six to ten hours. The regenerated epithelium of the skin does not form rete pegs, and the epidermodermal junction is therefore smooth.

Dermal Appendages. The hair follicles, sweat glands, and sebaceous glands do not regenerate if completely destroyed. However if the deeper ends escape destruction, there are restoration and establishment of continuity with the surface.

Specialized Glandular Epithelium. The liver is the best example of a specialized epithelial derivative with enormous powers of regeneration. In experimental animals removal of 75 per cent of the liver is followed by rapid proliferation of cells and restoration of the normal size within twenty-one to twenty-eight days. The regeneration is probably specific, that is, hepatic cells from hepatic cells and bile ducts from bile ducts. The salivary glands and the pancreas have much less capacity for regeneration, and destruction is usually followed by cicatrization. In younger animals both islands and acini of the pancreas may regenerate from intercalated ducts. The excretory epithelium of the kidney, especially that in the proximal convoluted tubules, re-

generates actively following injury such as by bichloride of mercury. Multinucleated masses of cytoplasm appear on the sixth to the tenth day, and by the twelfth to the twentieth day normal structure and function are restored.

normally present as slender elongated cells with small hyperchromatic nuclei become robust, with relatively large, spheroidal, vesiculated, lightly chromatic nuclei. As the numerous processes of cytoplasm are retracted and

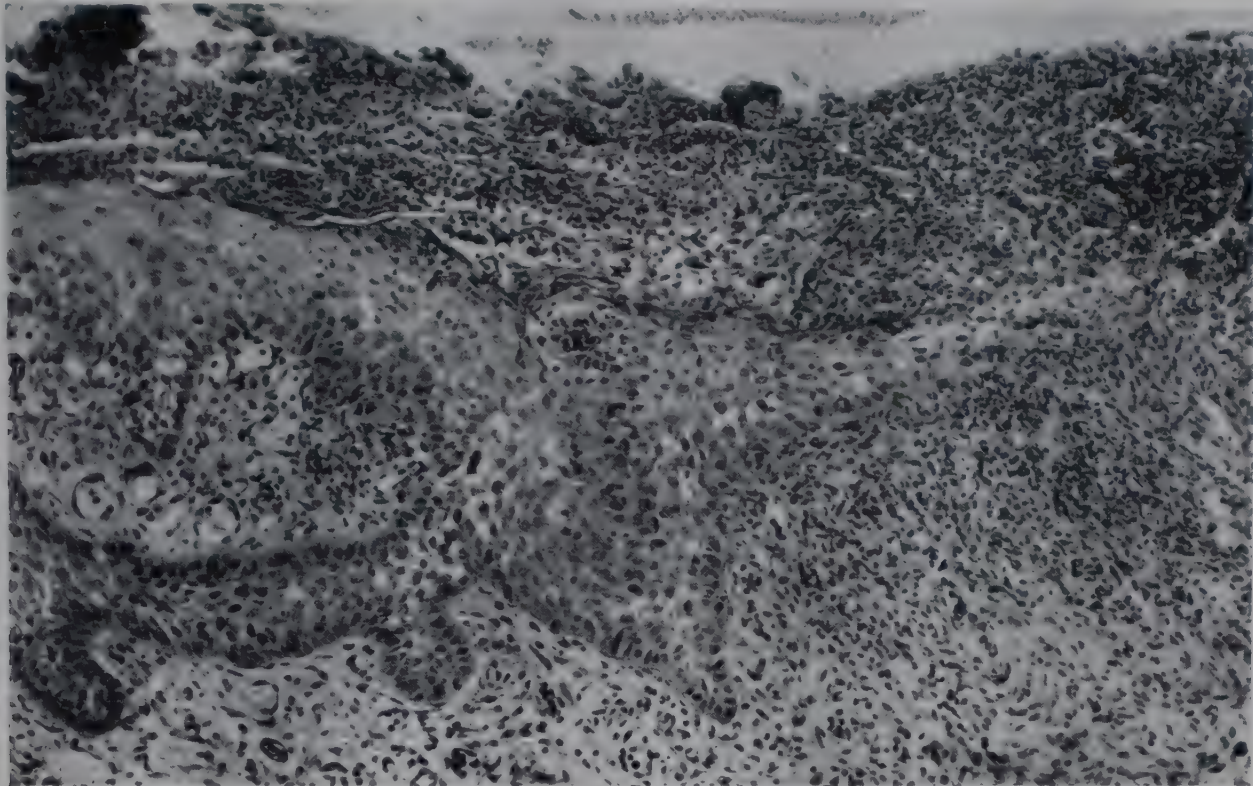


Fig. 67. Epithelium extending between the tissue and a scab in the repair of a defect in the skin of a rabbit's ear. (Tissue by courtesy of Dr. M. G. Seelig.)

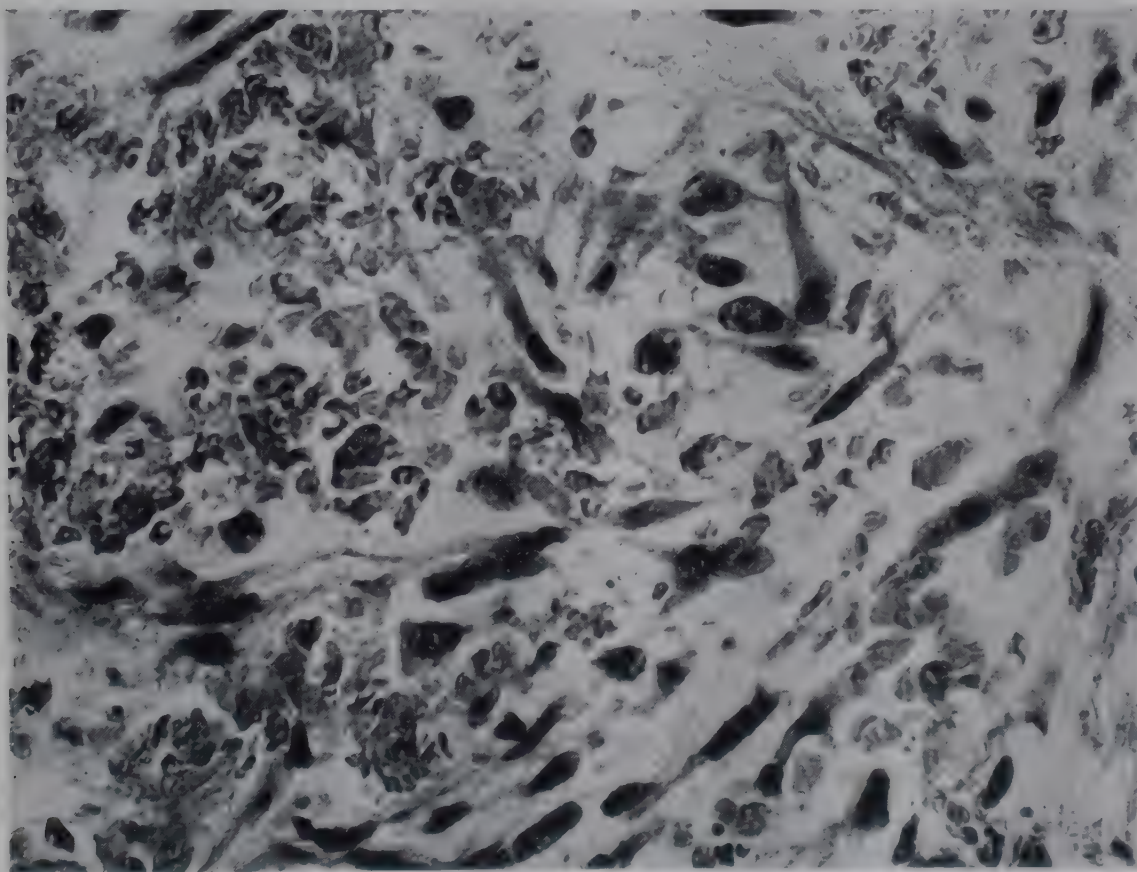


Fig. 68. Fibroblasts in a focus of hemorrhage. From the periaortic tissue three days after rupture of an aneurysm.

Fibro-elastic Tissue. Fibrous tissue composed of cells (fibroblasts) and of intercellular substance (collagen and elastic fibers) is the chief agency for the repair of defects in tissue. In an injured region the connective tissue cells

the cells become spherical, mitosis occurs. Each of the cells formed migrates along the threads of fibrin in the inflammatory focus. As the fluid and cellular exudate are removed, fibroglia are formed in the cells and the spe-

cific reticulin fibers appear in the intercellular spaces. Toward the end of repair, intercellular collagen is prominent, and the cells gradually revert to the resting fibrocytic type. In some scars, especially those subjected to repeated stretching, elastic fibers form, probably as a specific product of the fibroblast.

Adipose Tissue. Adipose tissue is a specific type of differentiated tissue and does not represent simply any group of mesenchymal derivatives with vacuoles of fat in the cells (Wells). It follows that regeneration of fat is

animals and in the human infant to ready availability and rapid metabolism.

Bone and Cartilage. Adult cartilage and bone do not regenerate, but the cells of the perichondrium and of the periosteum and endosteum retain the capacity to form new cartilage and bone under adequate stimulation. The space between the fractured ends is first filled with a blood clot, then with a fibrous callus, and finally with a bony callus. The details of the healing of a fracture are discussed in Chapter LVIII.

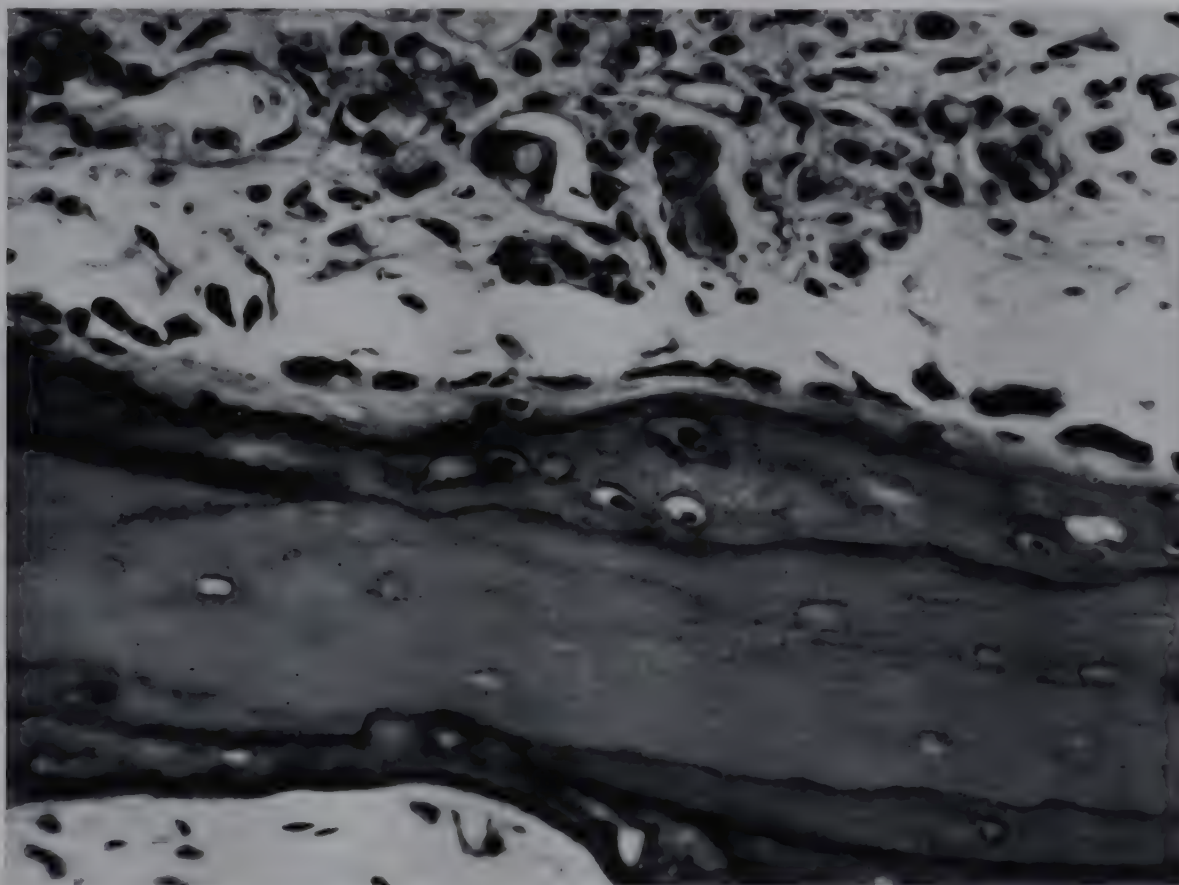


Fig. 69. Newly formed bone on an older trabecula.

from preexisting fat cells. In starvation the lobules of fat shrink and assume a typical appearance known as "serous atrophy." With resumption of normal dietary intake the cells again fill with fat. In traumatic injury the contained fat is hydrolyzed, and the liberated fatty acids stimulate the proliferation of fibrous tissue. In regeneration to fill a defect fat cells may occasionally be formed by metaplasia of fibroblasts.

Fat Glands. In the fetus and the young infant mesenchyme differentiates into lobules of adipose tissue. In certain places such as about the kidney, in the subcutaneous tissue between the scapulae, and in the neck, the lobules and lobes are prominent. The individual cells contain many small vacuoles of fat. Since the fat of all short-lived insects has this same fine dispersion, it is possible that it is related both in

In loss of adult cartilage not covered by perichondrium, such as articular cartilage, there is no regeneration, but replacement by fibrous or osseous tissue. Most newly formed bone is membrane bone, but endochondral ossification does occur, first by metaplasia of fibroblasts to chondroblasts and then by conversion of the cartilage to bone in the usual manner.

Heterotopic Bone. In many injuries, especially those associated with extensive hemorrhage, bone may form in the scar. The explanation is a local metaplasia of fibroblasts to osteoblasts. It is found in surgical wounds of the skin, in myositis ossificans, and in the calcification incident to the healing of foci of necrosis. Occasionally the spaces between the trabeculae are filled with typical marrow.

Muscle. Smooth Muscle. The capacity of

smooth muscle to regenerate is limited, except in certain tissues, to specific stimulation. In an incision of the wall of the intestine there is no regeneration, and the defect is filled with connective tissue. On the other hand in canalization of a thrombus the smaller vessels frequently develop media of smooth muscle, and it must be assumed that there has been true hyperplasia of smooth muscle cells.

During pregnancy, tremendous hypertrophy and hyperplasia of smooth muscle is seen in the enlargement of the uterus. This is in part the result of mitotic division of preexisting cells. In the stroma of the prostate and seminal vesicles excessive stimulation with estrogens will also provoke edema, hyperemia, and multiplication of smooth muscle cells.

Skeletal Muscle. Regeneration in skeletal muscle is limited. Following injury by trauma or by toxic substances in the blood, the necrotic cytoplasm appearing as a dense hyaline mass is removed by autolysis and by phagocytic cells. The interstitial fibrous tissue proliferates and fills the defect. The muscle fibers at the edge of the focus show distinctive changes. The fibers increase in length by addition of cytoplasm to the injured end, and myofibrillae are re-formed, apparently by addition to the ends of the preexisting fibrillae. The nuclei increase in number largely by amitosis, and multinucleated masses of cytoplasm appear. Finally cross-striations become visible in the newly formed fibers (Millar, Forbus). In minimal parenchymal damage as in Zenker's hyaline necrosis, there is apparently complete regeneration without scar formation (Forbus).

Cardiac Muscle. In adult persons hypertrophy of the heart is an increase in the size of each fiber. Quantitative studies show no increase in the number of fibers or in the number of nuclei (Karsner, Saphir, and Todd). In infants, however, hypertrophy of the heart is the result of an increase in the number of fibers and nuclei (Dammin and Moore). In necrosis of a part of the myocardium there is no regeneration, but multinucleated fibers and bizarre nuclei similar to those seen in skeletal muscle are present about the edge of the lesion.

Mesothelium. The flat cells lining the serous cavities rapidly multiply to cover a defect. The prevention of adhesions after injury to the peritoneum, pleura, or pericardium depends

on keeping the surfaces apart and retarding the proliferation of fibroblasts until the mesothelium has regenerated.

Blood and Lymph Vessels. The formation of new capillary blood and lymph vessels is almost unlimited but replacement of larger vessels does not occur. In granulation tissue solid endothelial sprouts grow out from preexisting capillaries. Soon fluid and cells are forced between the endothelium, a lumen is formed, and the surrounding fibroblasts serve as an adventitial framework. In the organization of a thrombus the endothelium of a vessel proliferates and grows into the thrombus; the isolated channels establish connections with one another to form a complete vessel through the thrombus. Regeneration of lymphatic capillaries is carried out in a similar manner (Coffin).

Blood and Bone Marrow. The red and white cells are constantly formed and destroyed, hence maintenance of normality depends not only on ability to regenerate but also on constant activity of the bone marrow. In an otherwise normal person, replacement of lost blood cells or production of increased numbers in response to an adequate stimulus is easily accomplished. Thus restoration of the total red cell count after a hemorrhage of 500 to 1000 cc. is attained in from one to three weeks in a normal person. On the other hand inadequacy of the chemical constituents for blood cells or damage to the bone marrow may limit the capacity for regeneration. In a young girl who is eating a diet deficient in iron, the relatively small loss of blood in menstruation may result in an anemia because the marrow is unable to respond in the absence of sufficient iron, and chlorosis results. Similarly injury of the bone marrow by benzene and other poisons, and by radiant energy, limits the normal replacement, and there is a progressively increasing anemia. The anemia of pernicious anemia and the leukopenia of neutropenia are based on the same phenomenon: inadequate formation because of the absence of specific maturation factors.

Extramedullary Hemopoiesis. In the fetus the blood cells are formed in the liver and spleen and in other tissues. As growth and differentiation proceed after birth, erythropoiesis and myelopoiesis are confined to the bone marrow. In severe anemia in adults, the liver and spleen may again assume a hemo-

poietic function. Small foci composed of a rare megaloblast, a few myeloblasts and myelocytes, and many normoblasts and erythroblasts are seen in the spleen and liver—a condition known as “extramedullary hemopoiesis.”

Lymph Nodes. If a part of the lymph node is destroyed, regeneration may take place, but frequently there is replacement by fibrous tissue. If an entire node undergoes necrosis, there is no replacement. The appearance of what are apparently new lymph nodes following loss of others is actually hyperplasia of preexisting small masses of lymphoid tissue which are present in all parts of the body.

Nervous Tissue. So far as can be determined, loss of a nerve cell is irreparable, but regeneration of a part of a cell such as an axon or a dendrite does occur.

Peripheral Nerves. If a peripheral nerve is cut, there are changes in all parts of the nerve and in the cells from which the axis cylinders take origin. Distal to the cut there is degeneration of the axis cylinders and of the myelin. The axis cylinders are swollen, fragmented, and granular. The myelin breaks up into small globules, which stain with the specific dyes. The cells of the neurolemmal sheath proliferate, and some apparently become phagocytic and engulf the degenerating myelin. There is a similar change in the proximal end for a distance of two or three nodes of Ranvier. The homologous ganglion cells show aggregation of the tigroid material, and slight chromatolysis. This type of reaction to injury in a peripheral nerve is known as “wallerian degeneration.”

If the two ends of the divided nerve are closely approximated, the axons grow back into the distal segment, and after from four to twelve months there is complete restoration of structure and function (Rivers and Head). It is interesting to note that the original experiments on tissue culture were undertaken by Harrison to prove that the processes of a nerve cell may grow out for long distances. If tissue is interposed between the ends or if the distal part is removed, as in amputation, the axis cylinders and neurolemmal sheath may grow to form a bulbous mass on the end of the cut nerve, designated as a “traumatic neuroma.”

Central Nervous System. Regeneration of axis cylinders in the central nervous system does not occur. A defect in tissue is repaired

by proliferation of astrocytes and fibrous tissue. The degenerated myelin and necrotic tissue are phagocytized by gitter cells derived from the microglia (Dunning and Furth). About the edge of the defect in the brain or cord astrocytes increase in number, fibrous tissue proliferates, and new capillaries are formed. If the defect is small, or if there is collapse of the walls, a solid scar of connective tissue and glia results. If the defect is large, a cyst filled with fluid and lined by glia and fibrous tissue is the last stage of repair.

General Considerations of Healing

The healing of wounds is a complex phenomenon which probably requires the coordinated activity of many agents and which is influenced by numerous factors both extrinsic and intrinsic (Arey). It is important for the physician and particularly for the surgeon to understand these factors in order that optimal conditions may be attained for the healing of wounds in man. Many patients requiring surgical operation have been sick for some days or months, and preoperative and postoperative treatment directed to the correction of deficiencies will materially accelerate the healing of wounds.

METHODS FOR MEASURING THE VELOCITY OF HEALING

Square Area of Wound Surface. The area of a wound in the skin may be traced on cellophane and measured with a planimeter or by weighing the cellophane. Observations with this method reveal four periods in healing: (1) latent period, (2) period of contraction, (3) period of epidermization, and (4) period of cicatrization.

Latent Period. In all tissues there is a latent period of one to seven days during which there is no change in the tensile strength of wounded tissue. This lag period is a basic biologic phenomenon occurring in all animal and plant organisms, including the protozoa and the bacteria. It corresponds to the time taken for the fibroblasts and capillaries to grow along the fibrinous network and bridge the defect with tissue (Carrel and du Noüy). It is during the latent period that the integrity of the closure must be maintained by sutures.

Period of Contraction. Contraction is active at first, slows progressively, and becomes re-

duced to zero when the edges of the wound are 10 to 15 mm. apart. Contraction is the result of the absorption of fluid and shrinking of the clot of fibrin in the defect.

Period of Epidermization. Soon after injury the epithelial cells about the edge of the wound increase in size and multiply rapidly. Within a short time tongues of epithelium extend over the denuded surface and join those from the other sides to form a complete covering. If the edges are more than 10 to 15 mm. apart, complete healing is not possible and skin grafts must be used.

Period of Cicatrization or Maturation. The period of gradual conversion to a dense, relatively avascular scar extends over a long time—weeks or months. In this stage the fibroblasts deposit collagen and the numerous capillaries of granulation tissue decrease in number.

Tensile Strength. The apparatus used in industry to test the tensile strength of thread is applicable to the determination of the strength of wound closures. Tissue which has been incised and sutured is removed after a selected interval, and the pull necessary to rupture the wound is ascertained (Howes, Sooy, and Harvey). In the hollow viscera a variant—the pressure within the lumen needed to disrupt the wound—may be used. Measurements by this method show (1) a latent period, (2) a period of rapid increase in tensile strength, and (3) a period of gradual return to normal.

Mathematical Expression of the Velocity of Healing. Du Noüy has from direct observations calculated a mathematical formula with which the degree of healing in a wound may be predicted.

$$\text{Log } S_T = \text{Log } S_0 - K \left(T - \frac{T^2}{2p} \right)$$

when S_0 is the observed size of the initial wound, S_T the observed size of the wound at time T and K is a constant.

$$K = \frac{\text{Log } S_0 - \text{Log } S_T}{T}$$

$$2p = \frac{T^2}{a}$$

$$a = \frac{\text{Log } S_0 - \text{Log } S_T}{K} - T$$

FACTORS INFLUENCING THE VELOCITY OF HEALING

Protection. A wound completely protected from mechanical, chemical, and bacterial irritation does not heal for many days. The latent period in cicatrization is greatly shortened if an irritating agent is applied to the surface or if the wound is slightly infected. It thus appears that the stimulus for cicatrization under ordinary conditions is not an internal factor. The reported beneficial action of pressure dressings is probably based on the same mechanism.

Nutrition. Protein. A high protein diet has no influence on the duration of the latent period, but once the growth of cells is well under way the velocity is distinctly increased. The maximal strength of wounded tissue in an animal on a high protein diet is attained about two days earlier than in animals on a standard diet (Harvey and Howes).

Vitamin C. The deposit of collagen by fibroblasts and hence the strength of fibrous tissue depend on an adequate supply of Vitamin C. Wounds in scorbutic animals and in patients with scurvy do not heal normally. In patients with disrupted wounds the average values of plasma ascorbic acid and serum protein are significantly lower than in normal persons (Hartzell, Winfield, and Irvin; Glenn and Moore).

Vitamin D. There is no satisfactory evidence concerning the influence of vitamin D on the healing of wounds of soft tissue, but in the healing of fractures there seems little doubt that the rapidity of callus formation and the strength of the callus may be increased by an adequate but not an excessive intake of vitamin D. Similarly the calcification of the caseous nodule in first-infection tuberculosis in rabbits is accelerated by the addition of vitamin D to the diet.

Temperature. In poikilothermal animals between the range of 23° and 38° C. the rate of cicatrization is increased twofold for each 10° C. This is the temperature coefficient of chemical reactions of the first order and of most biologic reactions (see the discussions of phagocytosis [p. 108], chemotropism [p. 106], and the effect of fever on metabolism [p. 167]). It follows that the velocity of healing depends on the metabolic rate of the tissue (Ebeling). Direct measurement of the respiration and anaerobic glycolysis of heal-

ing wounds shows that there is a definite increase (Von Gaza and Gissel).

Size of the Wound. The velocity of cicatrization of an aseptic wound is greater at the beginning than at the end of the period of repair, and there is a constant relation between the size of the wound and the rate of healing. Thus two wounds of different size have a tendency to become equal in size (Fig. 70) (Carrel and Hartmann), but the rate of

Absorbable suture material is digested by the same enzymes of the plasma and cells that dissolve the elements of the exudate; hence the higher the concentration of enzymes, the more suppuration there is, and the greater the exudation of fluid and cells, the more quickly the catgut loses tensile strength. Prolongation of the strength of catgut is attained by chromicizing, but even chromic catgut will rapidly dissolve in the presence of in-

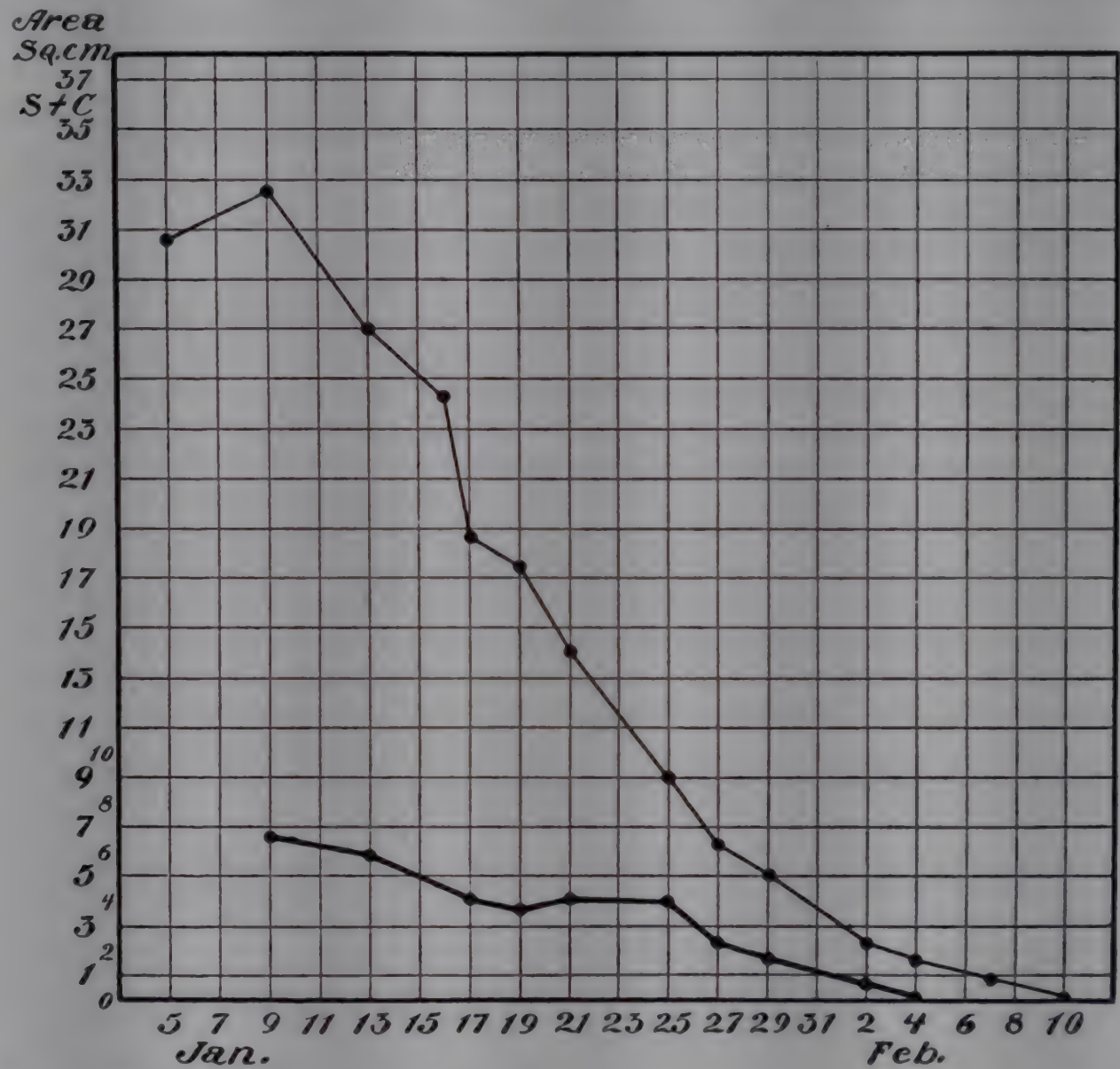


Fig. 70. A diagram illustrating the velocity of healing of two wounds of different initial size. (After Carrel and Hartmann.)

epidermization is greater in small wounds than in large (Spain and Loeb).

Suture Material. Wounds may be closed by absorbable sutures (catgut) or by unabsorbable sutures (linen, cotton, silkworm, wire, etc.). Even the most inert material is slightly irritating, and the amount of suture in the tissues influences the velocity of healing. Thus in a wound of the stomach the return to normal tensile strength does not occur as rapidly or as completely with No. 3 chronic catgut as with No. 000 plain catgut (Howes, Sooy, and Harvey). A further factor is the sensitivity of some persons to catgut (Langston).

fection (Jenkins, Hrdina, et al.). In one experiment in a noninfected wound, No. 2 chronic catgut proved to possess a tensile strength of 5 pounds on the sixteenth day, while in an infected wound the tensile strength had already reached the value of 5 pounds by the second day (Howes).

Infection. Infection is one of the chief factors that retard healing. This influence is exerted by prolongation of the period of destruction and increase of the amount of tissue destroyed, both of which delay the time of complete cicatrization.

The relation of syphilis to the healing of

wounds has important medicolegal implications. It seems probable that wounds through tissue not directly involved by the spirochete in a person with syphilis heal as rapidly as in nonsyphilitic persons. However, cicatrization and healing of a wound in a tissue already the seat of syphilitic inflammation are conspicuously delayed.

Endocrine Glands. There is a definite retardation of healing in animals from which the thyroid has been removed (Kosdoba), but the tensile strength of wounds of the stomach is not influenced by hypophysectomy (Mueller and Graham).

Radiant Energy. There is conflicting evidence on the effect of infra-red, ultraviolet, and roentgen rays on the velocity of healing. It appears that small doses in general stimulate cell proliferation.

Age. Wounds heal more rapidly in young than in adult animals. An analysis of this observation shows that the proliferation of fibrous tissue begins earlier and is less retarded in the young animal, but that the basic rate of fibroplasia is the same (Howes and Harvey). In man the rate of healing is directly proportional to the age, and may be expressed mathematically (Du Noüy). More careful studies of healing in senile animals are needed.

THE ULTIMATE STIMULUS FOR REGENERATION

The relative quiescence of adult cells may logically be attributed to either an active restraint of growth or a passive absence of a stimulus for growth. Studies with tissue cultures show that there is no obstacle to growth, hence there must be some substance in the tissues of younger animals and in tumors which stimulates the proliferation of cells. The expressed juices of embryonic tissue do contain a powerful stimulus. Investigation of the fractions of the embryonic juice reveals that the active agent is protein in nature, and that it is not free amino acid. Carrel and Baker conclude that the ability to promote growth is directly proportional to the ease with which the protein of a tissue can be transformed to peptides by enzymes. More specifically it can be shown that the sulfhydryl radical is one of the most essential stimulating agents (Hammett and Reimann).

PATHOLOGIC ANATOMY OF HEALING

It is apparent that the healing of all wounds must involve the same basic changes in tissue. However, the details vary with the size of the wound and the amount of destruction, so that it is convenient to discuss the pathologic anatomy of healing under two titles, "Primary Healing" and "Healing by Granulation." The differences between the two are relative, and there is no sharp line of distinction.

Primary Healing. In primary healing the destruction of tissue is minimal and the edges of the wound are accurately apposed, leaving no dead space which must be filled by granulation tissue. Primary healing is well exemplified in the clean, noninfected surgical wound of the skin. After the two surfaces have been brought together by suture material, the fat and other adjoining tissue expand, partly by their own elasticity and partly by the accumulation of fluid, so that the closure is complete. Between the two cut surfaces a small amount of fibrin and fluid collects, and this appears on the surface as a dry, gray or brown scab. By the second day, fibroblasts and endothelial sprouts proliferate along the threads of fibrin, and by the third day there is union of tissue from the two sides. The endothelial sprouts open and vascular continuity is reestablished. The fibrin is dissolved by enzymes, the edema subsides, the fibroblasts deposit collagen, and by the sixth to the tenth day there is complete healing. On the surface the epithelium migrates and proliferates to cover the defect.

Variants of primary healing involving only epithelium are seen in the healing of the superficial abrasions of the skin and cornea, and in the repair after vesiculation of the skin. In the cornea repair of epithelium is accomplished almost entirely by the migration of cells. In fact the number of mitoses demonstrable in the corneal epithelium following a minor injury is quantitatively decreased for several days. A vesicle of the skin involves the upper layers and separates the superficial from the deeper parts. The roof of the vesicle becomes necrotic, and an entirely new epidermis is regenerated from the basal layers, both under and at the edges of the vesicle.

Healing by Granulation. Larger defects, either on the surface or within a solid tissue, involve greater destruction of cells and require replacement by fibrous tissue. When viewed on the surface, this fibrous tissue after

a few days is seen to be composed of numerous small granules, 1 mm. in diameter, hence the name "granulation tissue." Each granule is composed of a central vascular core with

granulation tissue which gradually grows up from the base. Until this granulation tissue reaches the surface there is little reaction on the part of epithelium. As the epithelium

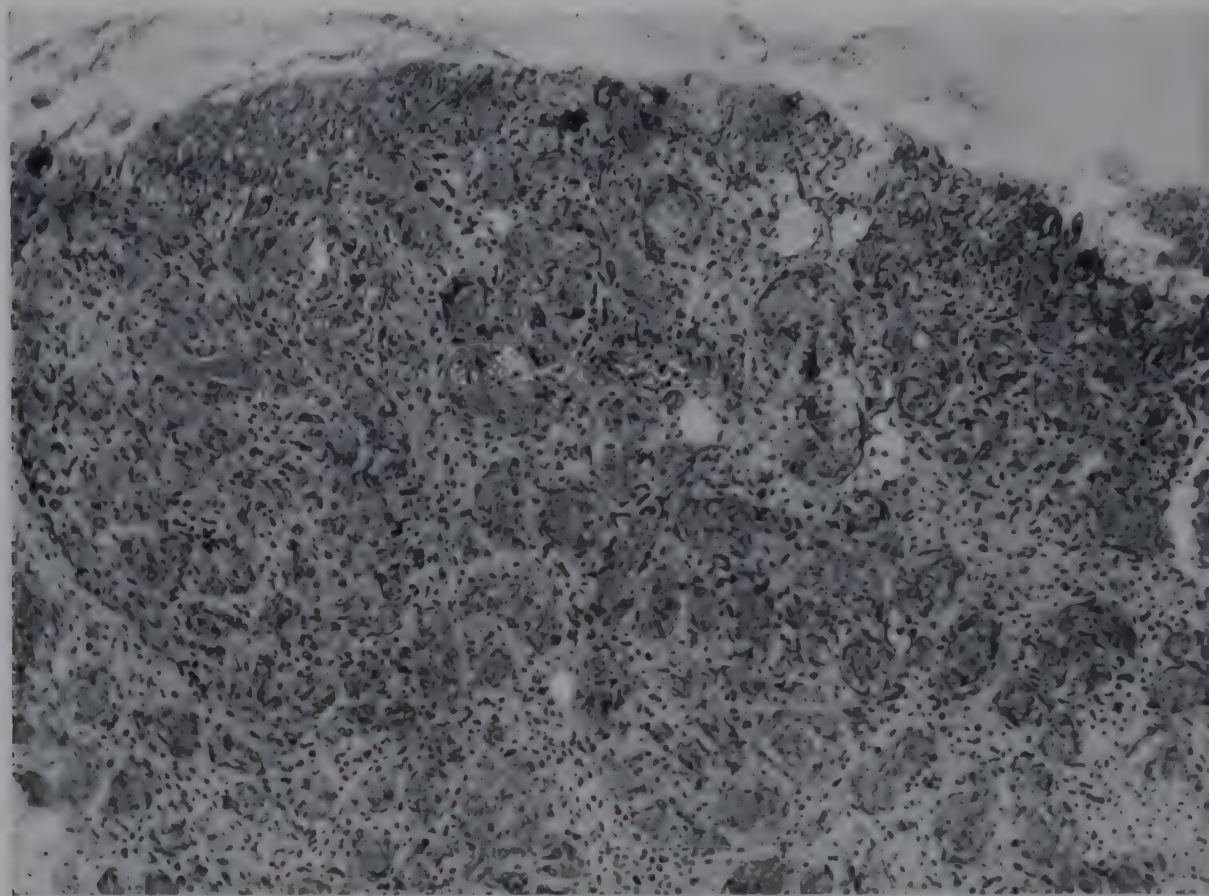


Fig. 71. Granulation tissue.

proliferating fibroblasts and wandering cells in the intervascular spaces. Early there is no differentiation of the vascular tree into an arterial and venous side, but there are con-

starts to proliferate, a delicate bluish, translucent zone about the edge with a sharp, irregular, inner margin can be seen. The fibroblasts serving as adventitia for the sprouting

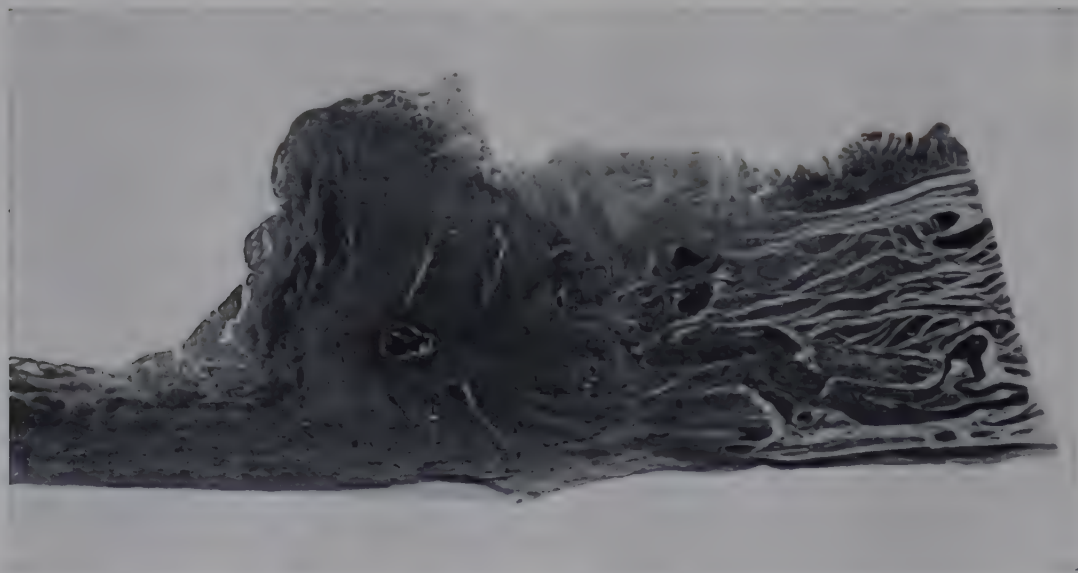


Fig. 72. Healed wound of a cholecystogastrostomy.

tinuous capillary loops originating from adjacent living vessels.

In a large wound of the skin, extending into the deeper structures, repair involves filling of the defect and reestablishment of epithelial continuity. The defect is filled by

capillaries deposit collagen, and a scar finally results. With maturation of the scar the rich vascular network of granulation tissue gradually disappears, the collagen contracts, and the dense, firm, relatively avascular scar is the result.

The reaction of epithelium involves two basic processes: the migration of cells and proliferation of cells. In smaller wounds the process is apparently one of migration such as has been described in a preceding paragraph about the cornea. In larger wounds—those in which the defect measures from 5 to 10 mm.—there is active hypertrophy and hyperplasia. The epithelial cells at the edge of the wound increase as much as 35 per cent in size, and there are many mitotic divisions. If a scab is on the surface (a scab is nothing more than a dry, fibrinous exudate), the reaction of the adjacent epithelium is somewhat different. In the more superficial layers large protoplasmic masses, free of nuclei or with multiple nuclei, spread into the scab and become densely adherent to the fibrin. In the deeper layers the cells proliferate and invade along the base of the fibrinous scab, and early do not establish a union with the granulation tissue. Thus if a scab is removed before healing is complete, the surface bleeds and the process of repair must start anew. With the passage of time the deeper epithelial layer becomes adherent to the proliferating connective tissue, and then the scab may be lost without disruption of the healing process (see Fig. 67, page 117).

In solid tissues the obliteration of a necrotic focus depends on the retention of a framework for the granulation tissue. In tissue culture it has been shown that fibroblasts grow along any delicate network, but do not grow into a fluid. In the edge of an abscess or infarct the formation of granulation tissue is identical with that in a wound of the skin. If the content of the cavity becomes liquid or is discharged into a hollow viscus, further healing must await the collapse of the cavity. Thus in chronic pulmonary tuberculosis, in which a relatively large focus of pulmonary tissue in the apex of the lung become caseous and is eventually discharged into a bronchus, final healing can only be accomplished if the walls of the cavity come in contact with one another. In small cavities this occurs spontaneously, but in larger cavities the surgeon must mechanically collapse the space. This principle is the basis for the treatment of tuberculosis by pneumothorax or by thoracoplasty. In solid tissues not adjacent to a hollow viscus, such as in abscess of the brain or

in an abscess of the deeper tissues of the extremity, the cavity filled with fluid gradually collapses by resorption of the fluid and pressure from the surrounding tissue, especially by the scar tissue formed in the wall.

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XII

General Pathology of Tumors

A neoplasm or tumor is an autonomous new growth of tissue (Ewing). Further qualifications only serve to obscure the basic phenomenon: a cell or a group of cells has broken through the normal restraints of growth and has become autonomous.

Nomenclature of Tumors

Tumors are named for the cell of origin by taking the root word of the cell and adding

lute, and many benign tumors may show some of the qualities of a malignant tumor, it is convenient to tabulate the contrasting potentialities (Table 3).

In order to emphasize that these qualities are relative and frequently not correlated, the following exceptions, among many, are noted. The glioma does not metastasize but does grow by invasion. Carcinoma of the fundus of the stomach metastasizes and grows by invasion, but has little general effect on the host until

TABLE 3. GENERAL QUALITIES OF BENIGN AND MALIGNANT TUMORS

Quality	Benign	Malignant
Mode of growth.....	by expansion (centripetal)	by invasion (centrifugal)
Encapsulation	present	absent
Rapidity of growth	slow	rapid
Invasion of vessels	absent	present
Metastases	absent	present
Destruction of tissue.....	usually inconspicuous	prominent
General effect on the host	usually not significant	usually significant
Degree of anaplasia	differentiated cells	undifferentiated cells

the suffix “oma”—fibroma, chondroma, etc. When two or more cellular types are present, the more prominent cell is placed last for emphasis—myxofibroma, lipomyxoma, etc. In some instances two varieties of tumor derived from the same cell apparently represent two stages in the embryologic development. To indicate this difference the suffix “blast” is inserted between the root and the terminal suffix for the more primitive, and the suffix “cyt” for the more differentiated—astroblastoma and astrocytoma.

Benign and Malignant Tumors. All tumors exhibit certain biologic properties of growth and behavior which make it possible to divide them into two categories: benign and malignant. Although this differentiation is not abso-

terminally; and a small benign tumor in a bile duct has more general effect on the host than many large malignant tumors.

Classification of Tumors

As pointed out by Ewing there are four possible bases for classification of tumors: causal, regional, histologic, and histogenetic. Until knowledge is adequate for a causal classification, the histogenetic classification is the most revealing and significant from the standpoint of pathology. It is based on the known or assumed origin of the normal cells and of the neoplastic cells.

Histogenetic Basis of Classification. After fertilization of the egg and the initial mul-

tiplication through the blastula and gastrula stages in the mammal, the daughter cells separate into two great groups: the trophoctoderm and the inner cell mass. From the inner cell mass three varieties of cells develop: (1) those of unlimited potentialities of differentiation, (2) those of limited capacity of differentiation, and (3) those which differentiate into only one cell type.

The *first variety* is normally represented by the sex cells of the new individual, but it is probable that similar cells are misplaced during development. Tumors derived from these are teratomas. They are more common in the gonads, but may be observed in any part of the body. The *second variety*, cells of limited capacity of differentiation, are collected in certain parts of the body as specialized cell masses, notably the tissue that forms the salivary glands and the nephrogenic ridge. Tumors originating in these structures thus contain several cellular types, but the composition is limited and definite. They are known as "mixed tumors." The *third variety*, unipotential cells, make up the great part of the normal animal organism. In most instances the daughter cells are identical with the mother cells, but occasionally metaplasia or prosoplasia may allow a limited transformation to other closely related types.

Upon this concept of mammalian embryology it is possible to outline a classification of tumors having the best features of both a histologic and a histogenetic approach.

CLASSIFICATION OF TUMORS

- I. Tumors of the trophoctoderm (*hydatidiform mole, chorio-epithelioma*)
- II. Tumors of the inner cell mass:
 - A. Tumors of pluripotential cells of unlimited capacity for differentiation (*teratoma*)
 - B. Tumors of pluripotential cells of limited capacity for differentiation (*mixed tumors*)
 - C. Tumors of unipotential cells of limited capacity for differentiation:
 1. Benign tumors from mesodermal derivatives:
 - (a) From mesothelium (*mesothelioma*)
 - (b) From mesenchyme:
 - Fibroblast (*fibroma*)
 - Chondroblast (*chondroma*)
 - Osteoblast (*osteoma*)
 - Myxoblast (*myxoma*)
 - Lipoblast (*lipoma*)
 - Blood vessels (*hemangioma*)
 - Lymph vessels (*lymphangioma*)
 - Lymphoid cells (*lymphoma*)
 - Myeloid cells (*myeloma*)

Monocytic cells (*histiocytoma*)
 Smooth muscle cells (*leiomyoma*)
 Striated muscle cells (*rhabdomyoma*)

2. Malignant tumors of mesodermal derivatives:
 - Connective tissue in general (*sarcoma*)
 - Endothelium (*endothelioma*)
3. Tumors from specialized mesodermal derivatives:
 - Adrenal (*tumors of the adrenal cortex*)
 - Kidney (*renal cell carcinoma*)
4. Benign tumors from general ectodermal and endodermal derivatives:
 - Surface epithelium upon a supporting connective tissue (*papilloma*)
 - Glandular epithelium arranged in acini (*adenoma*)
5. Malignant tumors from general ectodermal and endodermal derivatives:
 - Squamous epithelium (*epidermoid carcinoma*)
 - Transitional epithelium (*transitional cell carcinoma*)
 - Cylindrical epithelium of glands and surfaces (*cylindrical cell carcinoma*)
6. Tumors from specialized ectodermal and endodermal derivatives:
 - Nerve cells (*neuroblastoma and many other types*)
 - Glial cells (*glioma of several types*)
 - Chromatoblasts (*nevus and malignant melanoma*)
 - Enamel-forming cells (*ameloblastoma*)
 - Endocrine glands (*tumors of the thyroid, parathyroid, thymus, and pituitary*)

Incidence of Tumors

It is difficult to state accurately the incidence of cancer, but the statistical studies of Dorn for the United States may serve as the basis of general statements. About 230 new cases of cancer are diagnosed each year per 100,000 population. Dublin estimates that of every 100 white children born, 10 males and 13 females will die of cancer. About 150,000 persons in the United States die of cancer each year.

In the experience of the Memorial Hospital in New York 86 per cent of all neoplasms are malignant; and 90 per cent of the malignant tumors are carcinoma and 10 per cent sarcoma (Pack and LeFevre).

Organ System Involved. Sex. Although cancer may involve any tissue in the body, 48 per cent in white men and 74 per cent in white women occur in the digestive and genital systems. The figures of Dorn are given in Table 4.

Influence of Age. Although any tumor may

be observed at any age, most tumors have a peak incidence and are rarely seen at other periods of life. Tumors in early life tend to progress more rapidly, disseminate more frequently, and recur more often than do the same tumors in later life. The average age of all patients with sarcoma is ten to fifteen

cial or personal habits. For example the incidence of certain tumors in two races, the Malays and the Chinese living in the Dutch East Indies, shows a difference; but this may be caused not only by race but by diet and other personal habits. A comparison of the incidence in a single race in two different

TABLE 4. PRIMARY SITE OF CANCER

Organ System	Per Cent	
	Male	Female
Respiratory system	8	2
Urinary system	7	3
Buccal cavity	10	2
Skin	17	11
Digestive tract	36	23
Genital system	12	51
All other sites	10	8

years less than that of those with carcinoma—thirty-five to forty against fifty to fifty-five. There are relatively fewer malignant tumors in the prepuberal period of seven to fourteen years than at any other time of life. Certain tumors increase in frequency with increasing age to the full life span of man. The more

localities may give a more precise index of the effect of geographic location. Table 5 illustrates some of these points. The influence of racial habits is well illustrated in the extreme rarity of carcinoma of the penis in the Jewish race, a race which practices early circumcision almost universally. In contrast,

TABLE 5. INFLUENCE OF RACE AND GEOGRAPHIC LOCATION ON INCIDENCE OF NEOPLASMS

Tumor Of	In Malaysans in Dutch East Indies (Bonne). Per Cent*	In Chinese in Dutch East Indies (Bonne). Per Cent*	In Chinese in Peking (Hu and Ch'in). Per Cent*
Skin	29.8†	11.6	7.5
Uterus	10.8	19.3	15.6
Liver	9.1	14.6	0.2
Breast	7.4	5.9	4.5
Penis	3.6	5.2	5.3
Stomach	rare	9.4	0.5
Jaw and buccal cavity	4.4‡	rare	3.9

* The percentages are figured on the basis of all tumors reported in the quoted papers, some of which are omitted from this table.

† Mostly of the lower legs, developing in chronic ulcers.

‡ In betel-nut chewers.

important of these are melanoma and carcinoma of the skin, carcinoma of the mouth, and carcinoma of the prostate.

Influence of Race, Geographic Location, and Racial or Personal Habits. It is difficult or impossible to delineate the separate influences of race, geographic location, and ra-

carcinoma of the penis is one of the most common tumors of the Chinese, who are rarely circumcised. The effect of racial habits is illustrated further (Table 6) in a comparison of the relative frequency of carcinoma in the gastro-intestinal tract in Caucasians in New York and in Chinese in Peking.

The influence of geographic location, climate, habits, and other factors is well shown in the differences in the death rate for white men in the United States in the North of 111 and in the South of 66 (Dorn).

On the other hand, there is a changing incidence. For example, in a twelve-year period between 1933 and 1944 there was a downward trend for carcinoma of the stomach, buccal cavity, skin, uterus, and liver, and an

of individual tumors will result from careful study of these separate factors.

Degrees of Malignancy—Grading of Tumors—Prognosis

All neoplasms termed “malignant” do not have the same capacity to invade, metastasize, and kill. Many attempts have been made to reduce these clinical observations to an ob-

TABLE 6. INFLUENCE OF RACIAL HABITS ON INCIDENCE OF NEOPLASMS OF THE GASTRO-INTESTINAL TRACT

Site of Carcinoma	In the Memorial Hospital (Pack and LeFevre). Per Cent	In the Peking Union Medical College (Hu and Ch'in). Per Cent
Esophagus	26.0	53.6
Rectum	46.7	19.6
Stomach	20.6	16.1
Colon	6.6	10.7

upward trend for cancer of the pancreas, testes, prostate, intestine, and lung (Potter).

Influence of Social Level and Occupation. Social level and occupation determine many activities of life. In general persons of lower social levels have a less adequate diet, both in total caloric intake and in the essential aliments. Cramer divided the people of England into five socio-economic groups (designating the highest as I and the lowest as V), and investigated the incidence of cancer of the upper alimentary canal and cancer of deep-seated parts of the alimentary canal:

	I	II	III	IV	V
Upper alimentary canal	33.0	45.6	56.0	57.8	79.3
Deep-seated types	16.5	17.8	16.7	14.2	16.3

It is thus apparent that social level has a profound influence on the incidence of carcinoma of the upper alimentary canal. A similar study of the mortality from carcinoma of the stomach in Bavaria shows an incidence of 38.8 in merchants, lawyers, and doctors, and 68.5 in agricultural workers.

Summary. From the discussion in the preceding paragraphs it is clear that certain carcinomas and sarcomas have a higher incidence in some parts of the world and in some types of persons. A survey of the varying causes of the differences in incidence emphasizes the fact that there is no one causal factor in tumors. Progress in the prevention

jectivity which is predictable and of value in determining prognosis. The criteria vary with the location and nature of the tumor, hence it is possible in a general discussion to cover only the broader aspects of the problem.

Degree of Anaplasia. All other factors being equal, the degree of anaplasia—that is, the departure of the cell from the normal adult type and hence similarity to embryonal types—is directly correlated with relative malignancy. The features observed microscopically are: special cellular type, nucleocytoplasmic coefficient, number of “pencil cells,” infiltra-

tive growth of cells, general type of tumor, irregularity in size of cells, irregularity in shape of cells, distinctness in outline of cells, chromatism of cytoplasm, functional activity of cells, irregularity in size of nuclei, irregularity in shape of nuclei, chromatism of nuclei, hyperchromatism of nuclei, number of mitoses and prophases, irregularity of mitoses, character of stroma, vascularity of stroma, type of cellular infiltration of stroma, and amount of cellular infiltration of stroma.

On the basis of these criteria tumors are designated as grades I to IV with I the least malignant and IV the most malignant.

Invasiveness. The cells of a malignant tu-

mor, in contrast with normal cells, have the capacity to infiltrate adjacent tissue. Coman and his associates have presented evidence that invasiveness is related to decreased ad-

tumor, and its formation is one of the outstanding potentialities of most malignant tumors. The mechanism by which the neoplastic cells reach the new region is varied, and

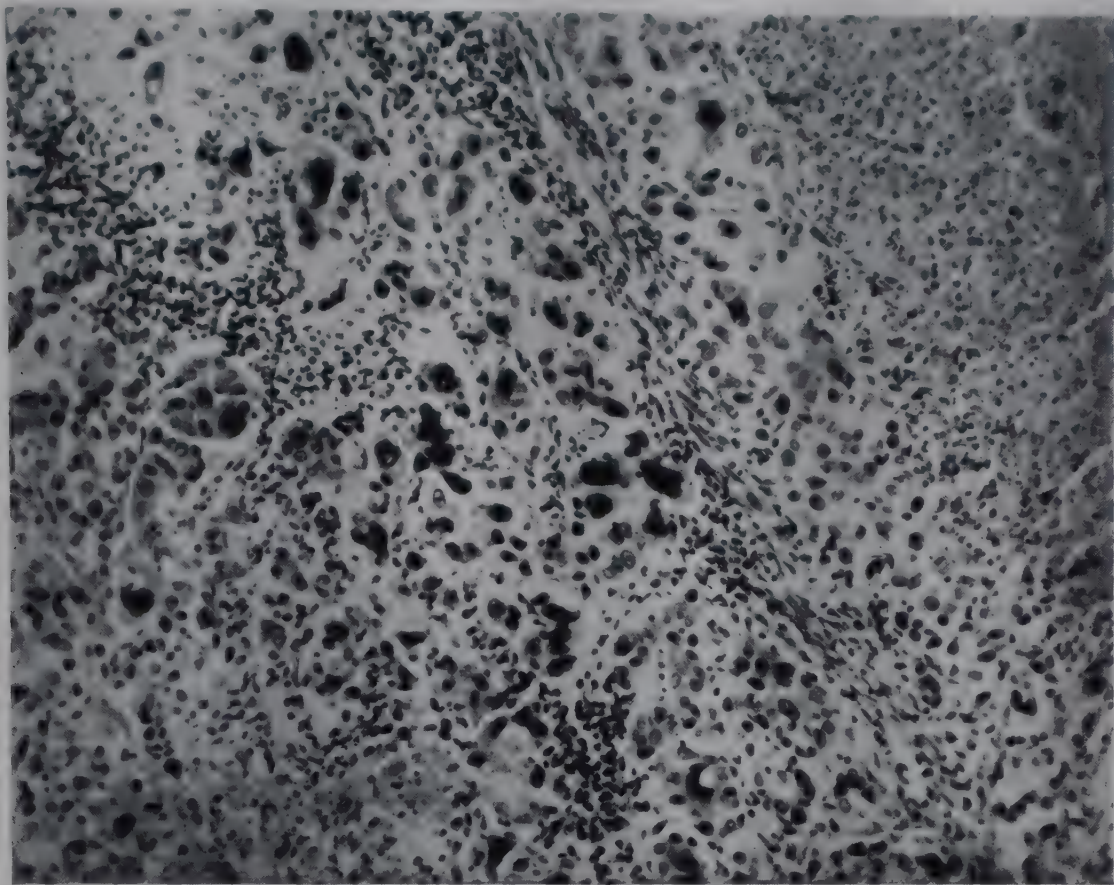


Fig. 73. Atypical epithelial cells in carcinoma.

hesiveness between cells, acquisition of capacity of ameboid movement, and liberation by the tumor cells of a spreading factor such as

will be considered under four categories ("Lymphatic Permeation," "Embolism," "Implantation," and "Contact").

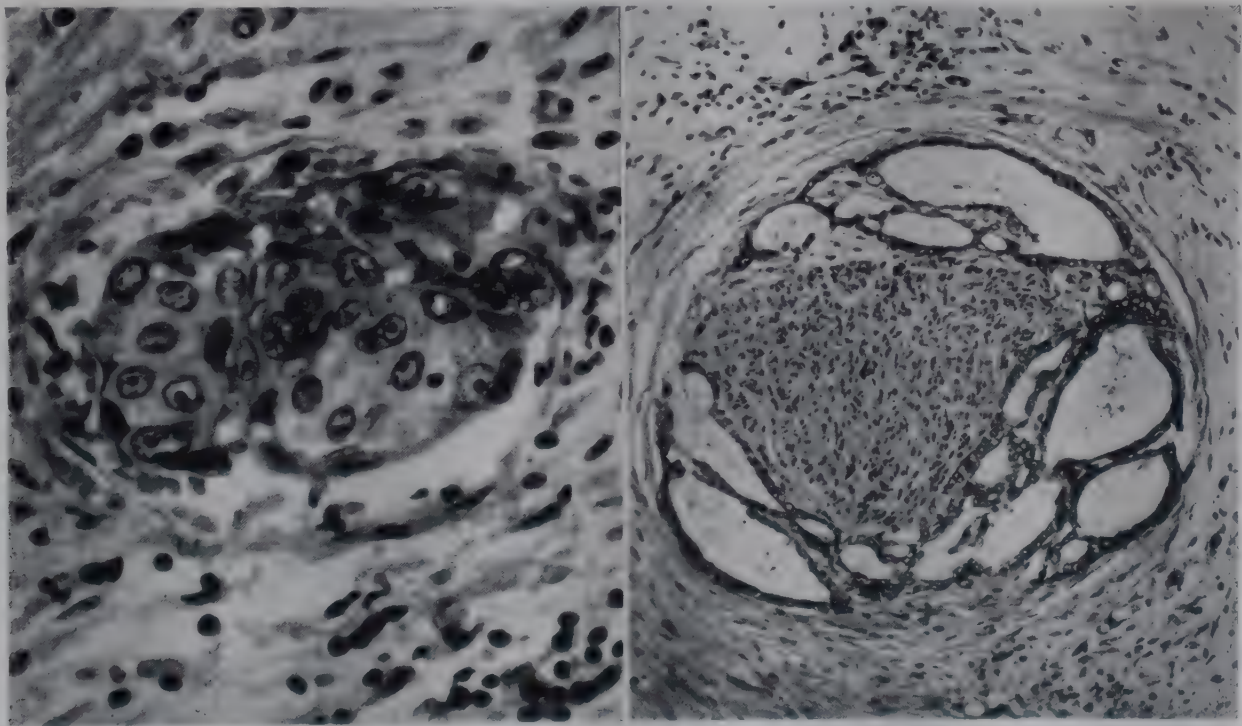


Fig. 74. Invasion of a small vein and of perineurial lymphatic by the cells of carcinoma of the pancreas.

hyaluronidase. The first, decreased adhesiveness, is probably related to reduction in intracellular calcium.
Metastases. A metastatic growth is a secondary tumor at a distance from a primary

Lymphatic Permeation. By "lymphatic permeation" is meant formation within a lymph vessel of a continuous column of neoplastic cells from the primary tumor to the secondary nodules. Permeation is acceptable as an ex-

planation of the small satellite nodules in the mucosa about carcinoma of the stomach or of the bronchus and of the multiple epidermoid carcinomas of the skin in a localized region in some patients. There is, however, some question that it fully explains distant metastases, although Handley, the most vigorous proponent of the theory of lymphatic permeation, has submitted much objective evidence in favor of it.

Embolism. In general, carcinoma metastasizes by the lymph vessels and sarcoma by the blood vessels; but exceptions are nu-

Lymph nodes draining a carcinoma may be enlarged, and show hyperplastic changes, for many months before actual metastasis occurs. Hence it is of the utmost importance to study all lymph nodes microscopically if a reliable prognosis is to be secured. In the node the first appearance of neoplastic cells is in the sinusoids, and with continued growth lymphatic tissue is compressed and invaded so that eventually there is only a spherical mass of tumor cells embedded in connective tissue.

Implantation. If a growing tumor reaches a serous surface or a hollow viscus, cells may



Fig. 75. Multiple metastases in the liver.

merous, and 5 to 15 per cent of all sarcomas show metastases in the regional nodes. This property is correlated with the microscopic appearance. In and about primary carcinoma invasion of lymphatics is more conspicuous than invasion of blood vessels, but both are seen. In many sarcomas vascular spaces are lined only by tumor cells, and malignant cells may fill a large sinusoid. Outstanding examples of vascular invasion are seen in chorioepithelioma of the uterus, in renal cell carcinoma, and in the malignant adenoma of the thyroid.

A type of metastasis frequently useful in diagnosis is the secondary nodule in a left supraclavicular lymph node in association with carcinoma of one of the abdominal viscera, referred to as "Virchow's node."

be cast off into the contained fluid and subsequently implanted in some other region. This is most frequently observed in the peritoneal cavity. The Krukenberg tumor of the ovary, a bilateral metastatic tumor, most frequently from the stomach, is the best example. With medulloblastoma of the cerebellum, cells escape into the subarachnoid space and implant over the spinal cord. In the urinary tract some examples of multiple papillary tumors of the pelvis and ureters undoubtedly represent implantation metastases.

The presence of tumor cells in effusions in serous cavities aids in diagnosis. The reliability of diagnosis is about 70 per cent, and is higher with pleural fluids than with ascitic fluids (Helwig).

Contact. A contact metastasis represents

the direct transfer of cells from a malignant tumor on one surface to an opposed surface such as might be assumed if an epidermoid carcinoma of the upper lip appears exactly opposite a preceding epidermoid carcinoma of the lower lip. It is apparent that proof of transfer as opposed to multicentric origin is almost impossible to secure. In dogs the venereal sarcoma is transferred by coitus (DeMonbreun and Goodpasture), but there is no evidence for sexual transfer of a malignant tumor in man.

Location of Metastases. The location of metastases in the regional lymph nodes is easily explained, but the tendency of certain tumors to metastasize to certain organs can-

in the lung, 45 per cent in the breast, and only 10 per cent in all other organs. In the entire series carcinoma of the lung and of the stomach constituted only 28 and 26 per cent respectively.

Relation of Size of Tumor, Duration of Tumor and Grade. The presence of metastases in the regional nodes at the time of treatment influences the prognosis unfavorably. Taylor and Nathanson have made an exhaustive study of this problem, and a few of their figures are quoted in Table 7.

Age. The younger the patient, in general, the poorer the prognosis. In carcinoma of the breast this influence of age on the grade of the tumor is well shown. In patients from

TABLE 7. PERCENTAGE OF METASTATIC TUMORS IN RELATION TO DURATION, SIZE, AND GRADE

	Carcinoma of Skin of Extremities of Trunk. Per Cent	Malignant Melanoma. Per Cent	Carcinoma of Lip. Per Cent
Duration:			
Short	11	57	14
Long	22	83	25
Size:			
Small	4	59	—
Large	27	55	—
Grade:			
Low	9	—	6
High	45	—	52

not be entirely explained. This localization is frequently useful in differential diagnosis. Tumors of the thyroid, kidney, prostate, and breast are more likely to metastasize to bone than any other tumors. The localization of the metastases of carcinoma of the bronchus in the brain, adrenals, and bone is well known. Detailed anatomic and physiologic studies should reveal the reasons for these differences. For example, metastases to the vertebrae from the prostate can be explained by true lymphatic permeation from the peri-aortic lymphatics, and cerebral metastases from abdominal carcinoma by retrograde transfer directly from the abdomen to the brain through the vertebral veins (Batson).

Metastasis in a certain organ frequently gives strong evidence of the site of the primary tumor. In fifty-three proved examples of metastatic carcinoma of the brain Baker found that 45 per cent were primary

eighteen to forty, 55 per cent were Grade III, while in patients from sixty-one to eighty only 32 per cent were of this high grade of malignancy (Taylor and Nathanson).

Stroma and Vascular Supply. All tumors possess a supporting framework of fibrous tissue and a vascular bed. The amount of both varies greatly. In some types of carcinoma there is excessive proliferation of dense collagenous connective tissue so that the tumor is extremely firm—scirrhou carcinoma. Other carcinomas excite little change in the surrounding fibrous tissue and hence are large, bulky, and soft—medullary carcinoma. In general the latter is the more malignant. The vascular supply of some tumors, especially osteogenic sarcomas, is rich, and these are frequently referred to as “telangiectatic sarcomas.”

Degeneration and Inflammation. All of the degenerative changes and types of inflamma-

tion described in the preceding chapters may be observed in neoplastic cells and tissues. Necrosis from pressure, hemorrhage, infarction on the basis of inadequate supply or twisting of the pedicle of a pedunculated tumor, and edema from milder circulatory disturbances are common. Pressure atrophy and fibrosis in the tissue immediately about an expanding tumor are to be expected. Infiltration with lymphocytes or eosinophils is usually associated with a high degree of malignancy. Bacterial inflammation of tumors which have ulcerated onto the surface is a serious complication.

Mode of Origin. Since no one has ever seen the first cellular multiplication which might be regarded as neoplastic, it is not possible to decide whether cancer takes origin from one cell or from a small group of cells. On the other hand serial or step sections of entire organs and of small carcinomas show clearly that many tumors have a multicentric origin. After establishment of a tumor, further growth is largely by multiplication of pre-existing neoplastic cells, but occasionally the microscopic appearance suggests growth by conversion of surrounding cells to tumor cells.

Summary. It is clear that a reliable prognosis in any given patient must rest on a judicious, correlated evaluation of all possible lines of evidence—age of the patient, general condition of the patient, size of the tumor, presence of metastases, histologic type and grade, location of tumor, and other less definable qualities.

Causes of Tumors—Experimental Tumors

To say that nothing is known about the causes of tumors is to ignore the tremendous advances made in cancer research since 1920. Medicine is today in possession of knowledge adequate to prevent many tumors. A part of this knowledge has come from clinical and anatomic study of tumors in man, and a part from investigation of both spontaneous and experimentally produced tumors in animals. It therefore seems advisable to discuss these two subjects as a single topic, and to divide the known and assumed causes into extrinsic and intrinsic factors.

Extrinsic Factors. The extrinsic causes of cancer may be classified into physical agents, chemical agents, living agents, and diet.

Physical Agents. **MECHANICAL TRAUMA.** There are many reports of the appearance of neoplasms after single or continued mechanical trauma, but in few is the cause-and-effect relation established. Warren defines the criteria as: "First, the integrity of the tumor site prior to injury must be established; second, the injury must be sufficiently severe to disrupt the continuity of the tissue at the site, and so initiate reparative proliferation of cells; third, the tumor must follow the injury by a reasonable length of time; and fourth, the tumor must be of a type which might reasonably develop as a result of the regeneration and repair of those tissues which have received the injury." The minimal acceptable time interval is about four weeks, and the maximal three years. In mice mechanical trauma to a region painted with methylcholanthrene does not accelerate the formation of a tumor. There is some evidence that mechanical trauma may change a benign to a malignant tumor, as in the transformation of a nevus to a malignant melanoma; and that trauma to a malignant tumor may facilitate the invasion of adjacent structures and the escape of cells to form metastases.

ULTRAVIOLET RAYS. The higher incidence of carcinoma of the exposed parts of the skin in the white race and in southern latitudes would indicate a relation to sunlight, presumably the ultraviolet rays (Blum).

INFRA-RED RAYS. Mice kept in a warm and humid atmosphere develop fewer spontaneous tumors, and the tumors grow more slowly. This is possibly correlated with the lower death rate by age groups from cancer in the southern United States than in the northern (Fuller, Brown, and Mills). Further proof of the relation of infra-red rays to the formation of cancer is given by the kangri-burn cancer of Tibet (Neve). The natives wear a heated brick in a basket on the abdomen, and epidermoid carcinomas of the skin appear in this region.

X-RAYS AND RADIUM RAYS. There is little doubt that both of these, if given in adequate doses, will produce carcinoma of the skin in man. The latent period varies from a few years to more than twenty years. There is first atrophy of the skin, and the carcinoma arises in the hyperplastic edge of the burn. In mice exposure to radiant energy in sublethal amounts will cause an increase in

leukemia and in functional tumors of the ovary (Furth and Furth).

Chemical Agents. Modern investigation of the chemical causes of cancer dates from the description of Yamagiwa and Ichikawa of epidermoid carcinoma developing on the ears of rabbits painted with coal tar.

CARCINOGENIC SUBSTANCES. In the latter part of the 1920's a group of chemists and biologists in the London Free Cancer Hospital demonstrated by spectroscopic study and differential isolation the carcinogenic activity of dibenzanthracene. Since then

bank), carcinoma of the bladder in workers in the aniline dyes (Ferguson, Gehrmann, Gay, Anderson, and Washburn), carcinoma of the bronchi in the miners of the Schneeberg (Schmorl), and leukemia in those working with benzene and arsenic (Hueper; Franseen and Taylor).

TOBACCO. In a high percentage of cases of carcinoma of the lip and buccal cavity there is a history of the use of tobacco (Bröders). A sharp separation of the effects of mechanical trauma from the pipe, the heat, and the tars of tobacco cannot be made. There is



Fig. 76. Papilloma and carcinoma of skin of rabbit. (Photograph by courtesy of Dr. Peyton Rous and Dr. John Kidd: J. Exp. Med., Vol. 62.)

many other pure substances have been shown to be carcinogenic, notably methylcholanthrene and 3,4-benzpyrene.

CARCINOGENIC SUBSTANCES IN THE BODY FLUIDS. Extractives of urine, of bile, and of liver tissue from patients with or without cancer have produced malignant tumors on subcutaneous inoculation into mice (Steiner). The urine of patients with myeloid leukemia contains a substance causing myeloid metaplasia of the spleen in guinea pigs (Heinle, Wearn, Weir, and Rose). It must remain for future study to place these facts in their proper relation.

OCCUPATIONAL TUMORS IN MAN. In man many tumors are known to be produced by chemical substances: carcinoma of the skin in the chimney sweeps of England and in the mule-spinners of textile mills (Brock-

some evidence that carcinoma of the bronchus is more common in heavy smokers (Graham and Wynder). In mice and rabbits tobacco tars induce the formation of papillomas, but rarely if ever a true carcinoma (Flory).

CONDITIONAL NEOPLASTIC STATES. It appears that chemical agents such as tar may render many more cells neoplastic than ever develop into tumors. A further mild stimulus months or years later, such as wound healing, will then suffice to make some of these conditional neoplastic cells multiply and form tumors. This mechanism may explain the appearance of cancer soon after an acute injury (Rous and Kidd).

Living Agents. **VIRUSES.** Rous in 1910 established that certain tumors of fowls may be produced at will by the injection of a cell-free extract of a tumor. Since then many

types of neoplasms in fowls have been described, and in each instance the filtrable agent is specific, and provokes the same pattern of neoplasm on continued inoculation. An adenocarcinoma of the kidney of the frog, and several varieties of tumors in fishes, have also been shown to be caused by a virus (Lucké and Schlumberger).

Gradually a number of neoplasms of mammals have also been established as viral in

servation, mostly without success. It is probable that Fibiger observed largely metaplasia and hyperplasia caused by vitamin A deficiency (Klein and Palmer). In man infestation with *Schistosoma* in Egypt is frequently associated with carcinoma of the bladder, and in the Orient with carcinoma of the colon.

Diet. Caloric restriction decreases the incidence and rate of growth of all experimental tumors, but relative deficiency of proteins and fats in the diet has an effect on some and not on others (Tannenbaum).

VITAMINS. The nature of the dietary vitamins has an influence on the induction of experimental tumors of the liver. Rats fed *o*-aminoazotoluene or *p*-dimethylaminoazobenzene (butter yellow) develop primary carcinoma of the liver, but an adequate ingestion of rice bran extract, yeast, or yeast extract reduces materially or prevents the appearance of tumors (Sugiura and Rhoads). It has been claimed that the action is a nonspecific one in preventing the absorption of the chemical. Here then is an example of a dual cause of a specific cancer—a toxic substance acting on an animal with a vitamin deficiency.

Intrinsic Causes. Heredity. Evidence for and against the role of heredity in the causation of tumors may be arranged in three categories: the occurrence of tumors in families, the occurrence of tumors in twins, and the occurrence of multiple tumors.

CANCER FAMILIES. One of the most carefully studied of the many cancer families which have been described is that reported successively by Warthin and Weller. Of 305 descendants of the paternal founder of the family, 174 had attained the age of twenty-five years in 1935, and 41, or 23.6 per cent, of these developed carcinoma (Hauser and Weller). These data provide strong presumptive evidence for an inheritable, organ-specific predisposition to carcinoma.

One of the most striking of the familial tumors is retinoblastoma of the eye in children, which may be expected to occur by chance in one of each 34,000 living newborn infants. In about 20 per cent of those afflicted bilateral tumors are observed—an incidence of one in 170,000 live births. The incidence reported by pure chance would be only one in 3,000,000. Thus bilateral retinoblastoma occurs nineteen times as frequently as would be expected. The familial incidence



Fig. 77. Tumor of a plant. (After Smith from Ewing.)

origin—papillomas of the skin (Shope) and buccal mucosa (Parsons and Kidd) of the rabbit, fibroma and myxoma of the rabbit, the infectious papillomas of man, dog, and cow, and the venereal sarcoma of the dog (Stubbs and Furth).

BACTERIA. No bacterium has been demonstrated as the cause of a tumor in an animal, but in plants the bacterium *Bacillus tumefaciens* is accepted as the cause of the focal hyperplasias known as "plant tumors" or "crown galls" (White and Braun).

METAZOA. Fibiger in 1913 reported the appearance of epidermoid carcinoma of the fore-stomach of rats infested with a nematode worm, *Gongylonema neoplasticum*. Many attempts have been made to duplicate this ob-

is shown by the collected reports of 102 children with retinoblastoma in 19 families (Weller).

TUMORS IN TWINS. Dizygous twins have a dissimilar total heredity which may be similar in some respects, while monozygous twins have as identical a heredity as is possible in two human beings. There are reports of tumors in one or both members of 63 pairs of monozygous twins and 46 pairs of dizygous twins. Comparison shows that tumors in both twins are more frequent if the twins are monozygous (66.6 per cent to 20 per cent); that the same type of tumor occurs in a higher percentage of monozygous twins (55 per cent to 20 per cent); and that the average difference in age of onset is less in monozygous twins (seven months to twenty-two months) (Macklin).

MULTIPLE TUMORS. A person with one cancer is six times more apt to develop a second cancer than would be expected by chance alone (Lombard, Levin, and Warren). Clearly there is a predisposition or susceptibility to cancer in certain persons, which although not proved to be hereditary may be assumed so for the present. This higher occurrence of multiple malignant tumors is most conspicuous in neoplasms of the same organs, then in neoplasms of paired organs, then in neoplasms of the same organ system, and is least strikingly shown in unrelated organs.

HEREDITY IN TUMORS OF ANIMALS. Many investigators have spent the greater part of their lives in the study of tumors in mice, notably Leo Loeb, Little, Slye, Tyzzer, Bashford, J. A. Murray, and Haaland. From their work a number of generalizations can be drawn: (1) tumors occur more frequently in some strains of mice than in others; (2) differences in the incidence of tumors in a strain are usually maintained in succeeding generations; (3) there is evidence of some specificity of the site of the tumor which can be fixed within a strain; and (4) there tends to be a characteristic mean age at which tumors of a given site occur within a given strain. All types of leukemia in mice show the same factors as tumors do (see Little, Slye, and Lynch for literature). Beyond this it is not possible to go at present. A beginning has been made in similar studies with rats and rabbits.

EXTRACHROMOSOMAL FACTORS. THE MILK FACTOR. In 1936 Murray and Little reported that the incidence of mammary cancer in hybrid mice of low and high cancer strains depends on whether the mother comes from the low or high cancer strain. They concluded that some extrachromosomal influence is at work which causes the difference. Bittner showed that mice born of a high-cancer-strain mother and nursed by a foster mother of a low cancer strain developed fewer mammary tumors than did mice nursed on a high-cancer-strain mother. This influence is designated the "milk factor." There is evidence of a similar influence in leukemia in mice (Furth, Cole, and Boon), and possibly in carcinoma of the breast in women (Wood and Darling). The milk factor is present in breast, spleen, and other tissues, and has many properties of a virus.

Fetal Rests. One of the first theories of the origin of tumors, proposed by Connheim, was that neoplasms are derived from small masses of fetal cells misplaced during development. Two lines of anatomic evidence may be cited in support of the theory: (1) the demonstrated presence of rests in tissues and organs in which similar tumors are known; and (2) the appearance of neoplasms near or in association with congenital anomalies.

The best known fetal rests are the small nodules of adrenal cortex in the capsule and in the substance of the kidney. They are 1 to 4 mm. in diameter, bright yellow, circumscribed but not encapsulated, and are composed of columns of typical cortical cells. Small islands of cartilage in the periosteum and in bone are believed to be point of origin of a number of bone tumors. Focal collections of undifferentiated cells are observed in the brain and in the adrenal medulla. Some of the rests in the adrenal disappear; others become malignant tumors; others become benign tumors; and apparently still others develop into malignant tumors and then subsequently differentiate to become benign tumors (Cushing and Wolbach).

The demonstrated anomaly in the development of the retina in associated with retinoblastoma furnishes strong support for the fetal rest theory (Ch'in). Womack and Graham have found that minor anomalies of the lung are frequent in those with carcinoma of the bronchus.

The coexistence in the same tissue of a tumor and a congenital anomaly is not an uncommon occurrence. Notable are glioblastoma in tuberous sclerosis, and carcinoma in a branchiogenic cyst, in a Meckel's diverticulum, and in an accessory pancreas.

Cellular Relations. Age of Cells. The fact that most tumors first appear in the latter half of life naturally focused attention on the relation of senility to neoplasia. The average age of patients with carcinoma is 53.8 years and with sarcoma 38.2 years (Pack and LeFevre).

SENILE CHANGES. The involution of tissue with advancing age consists essentially of atrophy of parenchyma and quantitative and qualitative changes in the connective tissue. It has been postulated that these alterations remove the tension on cells so that they may proliferate, or isolate small masses of cells, which may then, under some other stimulus, become malignant. In prostatic carcinoma there is rarely neoplasia until the gland has started to involute (Moore) and conversely carcinoma as a complication of hyperplastic lesions of the prostate is unusual (Moore). In most instances, however, increasing age does nothing more than give the cells of the body a longer time to express themselves.

CHRONIC IRRITATION. In a similar way the occurrence of tumors in regions of chronic irritation and in chronic ulcers where isolation of cells might be expected has turned attention to cellular relations and tissue tension. Epidermoid carcinomas in varicose ulcers (Knox), in fistulous tracts (Lynch and Gross), and in the ulcers of lupus have been reported. It is estimated that about 80 per cent of all carcinomas in scars are in the scars of thermal burns, and this is more likely to occur if there has been a chronic persisting ulcer in the scar. The latent period may be as long as fifty years (Halford and Gotshalk).

Endocrine Glands. An appreciation of the role of the endocrines in the causation of certain cancers dates from the observation of Lathrop and Loeb that ovariectomy in early life of female mice from a high-mammary-cancer strain reduces the incidence of tumors to almost zero. Since the discovery of the estrogenic hormones about 1930, it has been shown that at least in mice the estrogens influence the incidence and structure of car-

cinoma of the breast and of the cervix. This was first demonstrated by Lacassagne, who produced mammary carcinoma in the male mice of a high cancer strain by injection of estrogens. This experiment has been repeated many times in male and female mice (Loeb). Epidermoid carcinoma of the cervix in some strains of mice has also been produced by injection of estrogens (Gardner, Allen, Smith, and Strong). In transplantable mammary adenofibroma in rats both estrogens and androgens influence the structure (Heiman and Krehbiel).

Just how the estrogens affect the origin of spontaneous tumors is not clear. Rapid breeding of certain strains of rats increases the incidence of carcinoma and adenofibroma of the breast (Bagg). In the Albany strain of rat, the members of which develop adenofibroma of the breast, there are certain abnormalities of the sexual cycle (Wolfe, Burack, and Wright). In mice there does not appear to be any recognizable difference in the sexual cycle in high and low cancer strains (Burns, Moskop, Suntzeff, and Loeb). On the other hand the mammary gland of a high-cancer-strain mouse reacts more readily to a given amount of estrogen. It thus appears that the hereditary factor in mammary carcinoma of mice consists in part of an inherited degree of responsiveness of the breast to stimulation.

In women the relation of ovarian function to mammary carcinoma is indeterminate. Most patients with a carcinoma of the breast give a normal past menstrual history, but the menses rarely are normal at the time of onset of the tumor (Taylor). In a rare patient receiving estrogens, carcinoma of the breast develops, but there is no proof of a cause-and-effect relation (Geist and Salmon).

The urinary excretion of alpha ketosteroids by patients with cancer differs from normal (Dobriner, Rhoads, Lieberman, Hill, and Fieser).

Injection of androgens in animals has not resulted in tumor formation, but the observation that castration or the administration of estrogenic substances to patients with prostatic carcinoma brings about improvement of some, suggests a relation between this tumor and androgens (Huggins and Hodges). An interesting effect is that estrogens produce interstitial cell tumors of the testes in certain

strains of mice (Hooker, Gardner, and Pfeiffer).

The relation of the other endocrine glands to neoplasia is not yet clearly defined.

Retention of Secretion. A high percentage of women with carcinoma of the breast give a history of some abnormality of lactation. Correlated studies in mice show that occlusion of the ducts will localize a tumor in that breast but will not cause the appearance of a higher incidence of tumors than is characteristic of the strain (Bagg). Similarly rapid breeding of rats without allowing the young to nurse will increase the incidence of mammary carcinoma.

Preceding and Concomitant Disease. "Pre-cancer." It has often been said that cancer never develops spontaneously in an otherwise normal tissue. There is a great mass of data to support this concept, and the preceding or concomitant disease is referred to as "pre-cancer."

There is the greatest opportunity to observe this phenomenon in the skin. The occurrence of carcinoma in the scars of thermal burns, lupus, varicose ulcers, and fistulas, and in chronic dermatitis from irradiation, mineral oils, tar, and arsenic has already been mentioned. Other more specific associations are in xeroderma pigmentosum (Councilman and Magrath), in Bowen's disease, in chronic atrophic acrodermatitis (Pack and Wuester), in senile keratoses, and in sebaceous cysts (Caylor).

In the viscera it is more difficult to be certain of the chronology of the lesions, but it has been observed that about 90 per cent of all carcinomas of the gallbladder occur in gallbladders with cholelithiasis, and that about 70 per cent of all carcinomas of the liver are in livers with cirrhosis.

It is perhaps significant that in most of these so-called "precancerous" lesions there is a process involving repeated or continued injury and attempted repair.

Summary. The facts and observations cited in the preceding paragraphs strengthen the conclusion that while there is no cause of tumors, there are causes of individual tumors. Tumors are highly conditioned diseases, dependent on a concatenation of factors. In one tumor one combination is operative, while in another a different combination constitutes the cause.

Chemical and Physiologic Aspects of Tumors

Many studies have been made of the chemical composition and physiologic activity of neoplastic tissue in the hope of discovering some distinctive feature. At the present time most of the observations are simply isolated facts, and no general picture of the metabolism of tumors has yet been crystallized. It would not be profitable to review here all of the conflicting work. The reader is referred to the book by Greenstein.

Blood Tests for Cancer. In patients with cancer as well as with some other diseases, there is a defect in the serum albumin. Most of the blood tests which have been devised depend on this abnormality (Huggins).

The Ultimate Nature of Neoplasia. As is so ably expressed by Rous, "... since what one thinks determines what one does, in cancer research, as in all else, it is well to think something." At the moment most of the facts fit best into the idea that a tumor represents an escape of cells from a combination of injurious agents which would otherwise eventually cause death of the cell. The escape is accomplished by the acquisition of a new form of metabolism which cannot be adversely affected by the injurious agents. Since the new metabolic process is not normal and is not subject to the usual restraints, the growth and multiplication of the cells proceed autonomously. In one instance continued physical trauma or chemical injury is operative, in another a virus acts, in another a dietary deficiency, and in still others a combination of factors.

General Clinicopathologic Correlation

The effects of a tumor on a host may be arranged in four categories: (1) mechanical effects from the presence of a space-consuming mass, (2) secondary effects of erosion onto a surface, (3) effects of absorption of the products of necrosis, and (4) effects of functional activity of the tumor cells.

Mechanical Effects. The site of origin of a tumor determines in large part whether or not there will be any mechanical effects. The newly formed tissue of a tumor must be accommodated to the available space. A glioma of the brain in an adult is within a solid bony case, and the demand for more space must be

met by destruction or atrophy of the brain. The increased pressure is reflected in herniation through the foramina and compression of the dural sinusoids (see Chapter CV, p. 930). A tumor of the mediastinum is within the thoracic cavity, which has limited powers of expansion. Hence there is compression of the softest tissue—the lung—and consequent increasing difficulty of respiration. Tumors originating in or near a hollow viscus bring about stenosis or atresia of the viscus. In the

those in a tumor which is ulcerated onto a surface. Principal secondary effects of ulceration are hemorrhage and infection.

A benign tumor such as a leiomyoma of the uterus, if it erodes into the cavity of the fundus, may become ulcerated, and over a period of months or years loss of blood may result in severe anemia. Occasionally an exsanguinating hemorrhage through the ulcer in a carcinoma in a hollow viscus is the immediate cause of death.

Infection gaining entrance through a surface ulceration of a tumor is not infrequently as demanding of treatment as the tumor. Infection in a carcinoma of a hollow viscus may cause necrosis of the wall and permit perforation.

Absorption of Products of Necrosis. Cancer Cachexia. Physicians since the earliest days of medicine have noted that patients with certain tumors which we now call “malignant” gradually lose weight and strength and become emaciated. Most examples of cancer cachexia can be attributed to the obstruction of hollow viscera by the tumor or to secondary infection and hemorrhage. It is probable that the absorption of the products of necrosis is the cause of the fever and leukocytosis occasionally observed.

Functional Activity of Tumor Cells. Most neoplastic cells lose the specific function of the cell of origin, but there are notable exceptions, especially in tumors of the endocrine glands. Hypersecretion by the eosinophilic cells of the adenoma of the pituitary is undoubtedly the cause of the overgrowth of bone and soft tissue so characteristic of acromegaly. Adenomas, malignant adenomas, and occasionally carcinomas of the islands of Langerhans, of the thyroid, of the parathyroid, of the medulla of the adrenal, and of the ovary, secrete the specific hormone which produces secondary changes of considerable importance (see Chapter XCVII, p. 855). The cells of most nevi and malignant melanomas retain the capacity to form melanin, and the brown or black color of these tumors is a valuable diagnostic sign.

Less conspicuous functions are the production of mucus by mucinous carcinomas, the elaboration of silver-positive granules by the carcinoid, the storage of glycogen and fat by the renal cell carcinoma, and the rare storage of bile pigment by the carcinoma of the liver.



Fig. 78. A large carcinoma of the colon with ulceration and obstruction. (Photograph by courtesy of Dr. Lauren Ackerman.)

gastro-intestinal tract this means a decreasing ingestion of food and consequent emaciation. In the respiratory tract there is chronic inflammation of the distal segment of lung. In any part of the body a tumor may press on blood vessels or nerves and thus produce secondary anatomic changes and pain. In contrast are tumors in what might be called “noncritical” regions of the body. Carcinoma of the fundus of the stomach does not usually obstruct the lumen significantly, and the patient remains in relatively good health until the last few weeks of life (see Chapter LXXXI, p. 659).

Erosion onto a Surface. In a tumor growing in a solid tissue, the signs and symptoms, both local and general, are quite different from

Diagnosis of Cancer from Exfoliated Cells

Many malignant tumors erode through the lining of hollow viscera and from the ulcerated surfaces so produced, cancer cells exfoliate into the lumen. For many years this characteristic of tumors growing in the walls of the serous cavities has been utilized in the diagnosis of cancer. Fluid present in the cavities is withdrawn, centrifugalized, and the cells in the sediment examined in sections or in smears.

The fundamental investigations of Papanicolaou and Traut on uterine cancer have shown that this technique may be extended to many other hollow viscera. The criteria for the recognition of cancer cells vary with the viscus, but in general clumping of cells, hyperchromatism of nuclei, prominent nucleoli, and mitoses are significant but not diagnostic observations.

The method is reliable in decreasing percentage in tumors of the female genital tract, the lower respiratory tract, the stomach, the urinary tract, the male genital tract, and the lower alimentary tract.

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XIII

Pathology of Special Types of Tumors

Although each tumor of each organ will be discussed or mentioned in the chapters devoted to the various organ systems, it is advisable to outline and describe a few of the more important types in this chapter. So far as feasible, the factual information will not be duplicated, and the page references will be given to the sections on special tumors, so that the reader may correlate the general with the detailed. If a tumor occurs only or predominantly in one organ, it is not described in this chapter.

Some individuals interested in tumors have failed to distinguish between a focal mass of tissue and a true neoplasm growing autonomously. Thus we have in the literature neoplastic designations for all sorts of lesions: xanthomas, which are local deposits of fat caused by a disturbance in the metabolism of lipids; simple hemangiomas, which are congenital anomalies; polyps of the nose which are inflammatory in origin; and keloids, which are an overgrowth of fibroblasts during repair. In the following sections an attempt will be made to separate these pseudoneoplasms and discuss them under the heading of related lesions.

Tumors of Fibrous Tissue—Fibroma; Fibrosarcoma

Pathologic Anatomy. The fibroma is a circumscribed, encapsulated, usually lobulated tumor, composed of gray or grayish white, opaque or slightly translucent tissue. The consistency varies from softness (fibroma molle) to extreme firmness (fibroma durum). If the tumor projects onto an epithelium-lined surface, the epithelium may undergo papillary hyperplasia (papillary fibroma).

The principal components of the fibroma are fibroblasts, interstitial substance, blood

vessels, and lymph vessels. As compared to normal connective tissue, the fibroblasts are larger and more numerous. The cytoplasm is abundant, and the nuclei are large, ovoid, and moderately chromatic. The amount of collagen varies greatly, but fibroglia can always be demonstrated with special stains (Fig. 79). Elastic fibers are typically few. Blood vessels may be of normal structure or may appear as large sinusoidal spaces. The lymph vessels are characteristically conspicuous and dilated.

In large tumors secondary changes are to be expected—hyaline degeneration, edema, necrosis, cyst formation, calcification, and ossification. Muroid degeneration in a fibroma should not be confused with the true myxofibroma (Geschickter and Lewis).

Incidence. Clinical Types. Distribution. Despite the ubiquitousness of connective tissue, pure fibromas are relatively rare tumors. The outstanding clinical types are fibroma of the tendon sheaths, of the sheaths of muscle, of nerve sheaths, of the periosteum of bone, of the ovary, and of the nasopharynx.

Fibroma of the Tendons and Tendon Sheaths. This is a rare type of fibroma, and is observed on the feet and hands and about the shoulders, elbows, and knees. It is sharply encapsulated, and is composed of dense collagenous connective tissue.

Nasopharyngeal Fibroma. This is a highly characteristic type of fibroma in young men. It arises in the region of the base of the skull or upper cervical vertebrae and projects into the posterior nasopharynx as a firm, extremely vascular, smooth tumor (fully discussed on p. 643).

Parosteal Fibroma. Benign tumors of the connective tissue associated with bone are rare. Most tumors which appear to be fibromas are really variants of the giant cell tumor,

healing bone cysts, or osteoid osteomas, with a richly collagenous matrix.

Ovarian Fibroma. Fibromas of the ovary usually arise in the lateral pole of the ovary and grow progressively to cause pressure

fibroma of nerves arising from either the endoneurium or the sheath of Schwann (full discussion on p. 956).

Mixed Types. In many parts of the body there is a concomitant neoplastic growth of

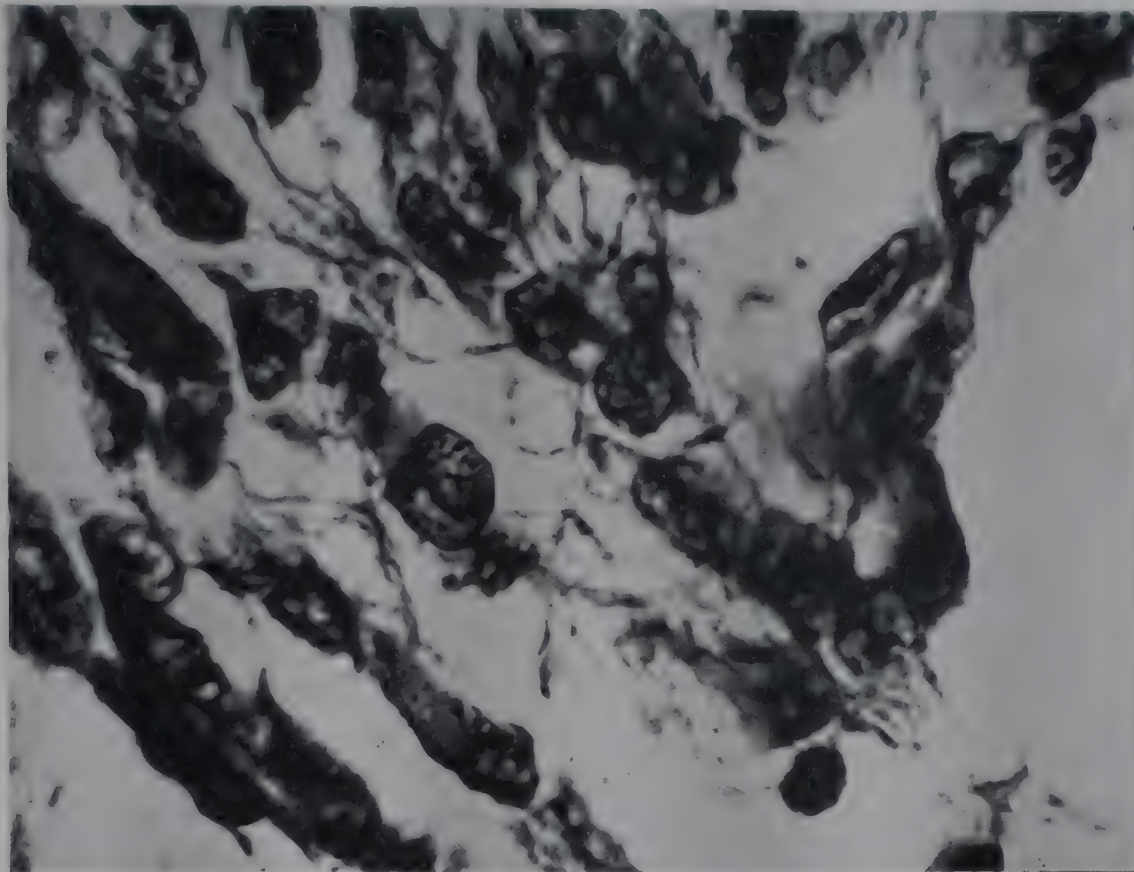


Fig. 79. Fibroglia in fibrosarcoma (stained with phosphotungstic acid hematoxylin).

atrophy of the entire organ. They should be differentiated from the histologically similar theca cell tumor (discussed on p. 887).

Fibroma of Fascias (Desmoid). The desmoid is a peculiar type of fibroma most common in the sheath of the rectus muscle of

fibrous tissue and of some other tissue or cell. The best known of these is the adenofibroma of the breast, which is fully discussed (p. 917) in the chapter on diseases of the breast.

Causal Factors and Pathogenesis. At least three factors appear to play a causative role



Fig. 80. Keloid. (Brenizer: Ann. Surg., Vol. 61.)

multiparous women of late middle life. It is not encapsulated, and there is invasion of the surrounding tissue (full discussion on p. 967).

Neurinoma. This is a specialized type of

in fibroma: an embryonic rest in a few, a scar in a considerable number, and familial predisposition in others, particularly neurofibromas.

Clinicopathologic Correlation. Fibromas

rarely grow to large size, so that the only complaint of a patient is the presence of a mass. Growth may progress continuously or intermittently. The nasopharyngeal fibroma blocks the airway, and because of the rich vascularity may bleed to the point of severe anemia. The ovarian fibroma is frequently associated with ascites, and occasionally with a right hydrothorax—Meigs' syndrome. Few fibrosarcomas arise in preexisting fibromas.

Related Lesions. There is no sharp line of distinction between hyperplasia of connective tissue in repair and neoplasia of fibroblasts; hence there are a number of conditions which resemble fibromas but which should not be so designated. Some use the term "pseudoneoplasms" for them.

Subepidermal Fibrosis. This nodular lesion of the skin is frequently referred to as a dermatofibroma, but is probably a reactive fibrosis and not a neoplasm.

Keloid. The keloid is a hyperplasia of fibrous tissue at the site of a previous injury. It may be sessile or pedunculated, and is more common in young adults, in women, and in Negroes; and occurs most often in the region of the sternum, neck, face, ears, arms, and back. The overlying epithelium is atrophic. The poorly circumscribed mass of connective tissue is composed of swollen, interlacing bundles of hyalinized collagen. Early there is moderate vascularity, but late the tissue is white, firm, and relatively avascular. Elastic fibrils are usually absent. Recurrence after removal is the rule, and there is a familial and racial predisposition.

Xanthoma. The small or large nodules of brownish yellow tissue in the dermis and other structures are seen as a part of other diseases, and occasionally as primary lesions. The basic defect is a disturbance in the metabolism of lipids, and a full discussion is given (p. 48) in the chapter devoted to that topic.

Hamartoma of the Kidney. Small, gray, nonencapsulated nodules, 2 to 5 mm. in diameter, are observed in the medulla of the kidney and occasionally in the cortex. Microscopically interlacing bundles of connective tissue, smooth muscle, and small lobules of fat are seen. They represent an anomalous development and are not true neoplasms.

Nasal Polyps. In many longstanding inflammations of the nose and accessory nasal sinuses, the mucosa becomes redundant and

the projecting folds take on the appearance of a tumor. The surface is covered by transitional epithelium or a single layer of columnar epithelium, and the entire mass is soft, gray, and translucent. In the center is a loose, mesenchymal type of connective tissue with stellate and spindle-shaped cells. Recurrence after removal is explained not as a neoplastic recurrence but as a result of the continued inflammation.

Fibrosarcoma. There are two important types of fibrosarcoma: that arising in the periosteum of bones (periosteal fibrosarcoma, p. 986) and that arising in the sheaths of peripheral nerves (neurogenic fibrosarcoma, p. 958).

There are all gradations between the fibroma and the fibrosarcoma, and it is frequently difficult to be certain of the distinction between the two. The fibrosarcoma is typically a bulky, soft tumor, composed of fleshy, grayish pink, finely fibrillar tissue. Foci of hemorrhage and necrosis are common. The cells are polygonal or spindle-shaped, and there is little intercellular collagen. Fibroglia are readily demonstrated. The nuclei are large and ovoid. Many mitoses are present in the more rapidly growing types. Invasion of surrounding structures is conspicuous, and recurrence after removal is the rule (Stout).

Tumors of Cartilage—Chondroma; Chondrosarcoma

Pathologic Anatomy. The chondroma is a firm, lobulated mass of bluish gray, translucent tissue, divided by connective tissue septa. Encapsulation is the rule, and the capsule contains a definite perichondrium, and in bones may have an outside layer of periosteum. Nutrition is carried on through blood vessels in the septa, and a rich lymphatic network. Muroid degeneration and development of cysts filled with a viscid fluid, calcification, and ossification are common. The structure varies from a close approximation to normal adult cartilage to an anaplastic mixture of stellate cells and of poorly developed matrix. The cells lack the orderly arrangement of resting or growing cartilage, and contain vacuoles of glycogen and fat. The matrix is irregular, and may be hyaline, fibrillary, or elastic.

Clinical Types. Distribution. The most

common chondroma is that of bone. Any bone may be affected, but the tubular bones of the hands and feet are the sites of predilection. The tumors are single or multiple in the periosteum or in the medullary cavity, most frequently in the diaphysis near the epiphysis, and usually make their appearance in the first three decades of life. The distinction between a true chondroma and ecchondrosis and a hamartomatous nodule of cartilage in the respiratory tract is not definite, and a diagnosis of a neoplasm of cartilage in these tissues must be based on clinical, macroscopic, and microscopic study.

Causal Factors. The occurrence of chondromas in early life suggests a disturbance in growth of cartilage as a basic cause. A familial incidence has been noted, and the occasional

rarely cause obstruction. Ecchondrosis of the bronchi on the other hand typically obstructs the lumen and leads to secondary changes in the lung (Moore).

Related Lesions. Ecchondrosis. An ecchondrosis is a single or multiple localized hyperplasia of cartilage, originating in preexisting cartilage. Some apparently possess or acquire neoplastic properties, and become true chondromas. The outgrowths are smooth, are composed of well ordered adult cartilage, and connect with the adjacent cartilage by fibrous tissue, perichondrium, or an isthmus of cartilage.

Hamartomatous Cartilage. In the bronchi and lungs, and less commonly in other tissues, small islands of cartilage become misplaced in development and persist as spherical nodules

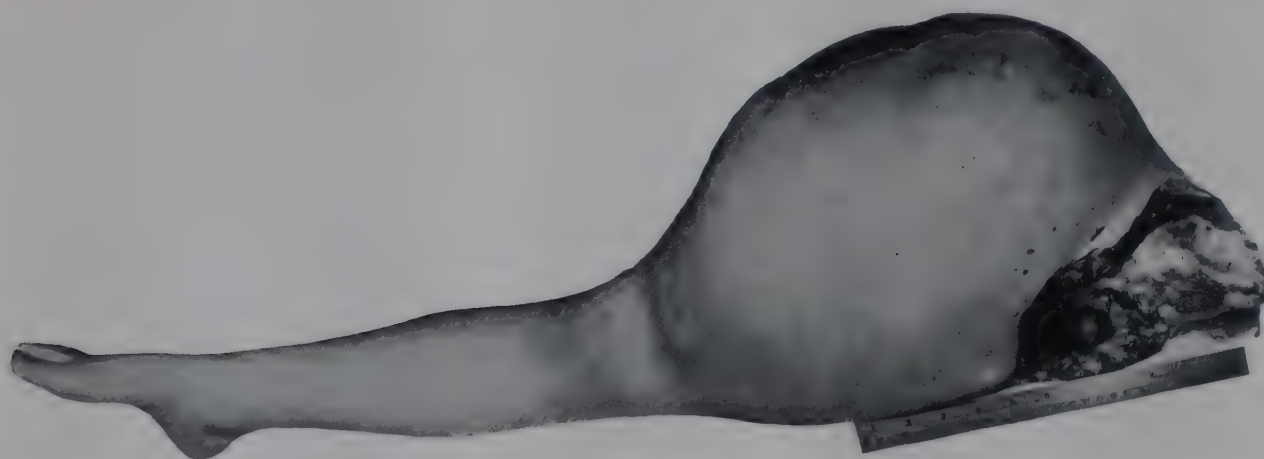


Fig. 81. Chondroma of the thigh.

observation of multiple chondromas of bone indicates a widespread constitutional anomaly of development.

Mixed Types. Islands of cartilage are important components of teratomas and of mixed tumors of the salivary glands and the kidneys. In a few chondromas a rich vascular network has led to the use of the term "angiochondroma." A true myxochondroma is frequently observed. Osteochondroma of bone is not an uncommon tumor, and should be distinguished from calcification and ossification in a chondroma and irritative ossification in the capsule of a pure chondroma.

Clinicopathologic Correlation. Chondromas grow slowly, and if multiple may produce deformities of the skeleton. In the medullary cavity there are gradual resorption of bone and fusiform enlargement, clearly demonstrable in a radiograph. Chondroma of the symphysis in women is a cause of dystocia. Chondromas and ecchondrosis of the trachea and larynx may deform these structures, but

(Hickey and Simpson). They are to be distinguished by the presence of elastic fibrils in the matrix. Admixture with deformed epithelial spaces, fibrous tissue, and fat is usual, and some have termed them "mixed tumors" (Womack and Graham).

Chondrosarcoma. In an evaluation of the malignancy of a tumor of cartilage the pathologist must consider many factors: cellularity, anaplasia of the cells, invasion of the capsule, and invasion of vessels. In general the softer, more invasive neoplasms are the more malignant. In the more undifferentiated tumors the identification of a matrix may be difficult.

Tumors of Bone—Osteoma; Osteogenic Sarcoma

The distinction between a true osteoma and many closely related non-neoplastic types of hyperplasia of bone is not sharp, and frequently an exact diagnosis cannot be made.

Pathologic Anatomy. What appear to be true osteomas are observed in the bones of the skull and the face. A smooth surfaced, eburnated, hemispherical mass of bone projects onto the external surface or inward into the orbit or accessory nasal sinuses. The structure varies from dense lamellar bone with few haversian canals to a spongy type of trabecular bone and bone marrow (Geschickter).

Osteoid Osteoma. This is a special type occurring in the trabecular parts of bones as a circumscribed tumor composed of sheets of osteoid tissue, partly calcified and ossified (full discussion on p. 983) (Jaffe and Lichtenstein).

Mixed Types. In many connective tissue tumors, especially those of cartilage, there is an intimate admixture with neoplastic bone, and the proper designation is "osteochondroma." In teratomas, bone may be a conspicuous feature, either as irregularly arranged trabeculae or as partially or fully formed bones. Ossification and foci of necrosis and calcification in other types of tumors should not be regarded as true mixed tumors.

Clinicopathologic Correlation. Osteomas rarely attain large size and hence are usually asymptomatic except for a palpable nodule.

Related Lesions. The macroscopic appearance of many focal hyperplasias of bone is frequently identical with that of an osteoma, and the differentiation must rest on clinical and microscopic observation.

Osteophyte. The osteophyte is a focal, usually solitary periosteal deposit of bone in the form of a diffuse plaque or nodule. It is seen in any region of periosteum which is affected by chronic inflammation. It consists of trabeculae of bone embedded in a richly vascularized, cellular fibrous tissue.

Hyperostosis. Hyperostosis is a more diffuse enlargement of bone. The surface is irregularly nodular. The best known example is hyperostosis of the internal table of the frontal bone in older women in association with mental disturbances (Moore; Henschen).

Exostoses and Endostoses. Circumscribed, smooth, flat, nodular or pointed growths on the periosteum and endosteum are usually observed toward the epiphyseal ends of the long tubular bones and especially about the insertion of tendons. The bone may be spongy or dense, and is usually capped by a layer of cartilage.

Osteogenic Sarcoma. The osteogenic sarcoma, a malignant tumor of osteoblasts, is more common in the long tubular bones of the extremities. The cells are pleomorphic, and there are numerous tumor giant cells containing two to six nuclei. The interstitial substance may be primitive osteoid, calcified osteoid, or well developed trabecular bone. The latter is present in the sclerosing osteogenic sarcoma with the characteristic perpendicular trabeculae on the periosteum. The gross appearance varies greatly from a grayish white, soft tissue, with destruction of bone, to a dense, calcified tissue of increased density. Foci of necrosis and hemorrhage are common, and in some tumors the vessels are conspicuous and are lined by tumor cells (full discussion on p. 985).

Tumors of Muroid Tissue—Myxoma; Myxosarcoma

The myxoma is a benign tumor of muroid tissue, typified by the muroid tissue of the umbilical cord. It is the only neoplasm occurring in adults of which the tissue of origin is not represented in the normal adult body (Stout).

Pathologic Anatomy. The typical myxoma is not completely encapsulated. The tumor is soft, lobulated, gray, and translucent. The cells are spindle or stellate shaped, and have anastomosing processes and a vacuolated cytoplasm. Between the cells is a stringy basophilic substance. Foci of hemorrhage, necrosis, and cyst formation are frequent.

Clinical Types. Myxomas occur chiefly in the subcutaneous and intermuscular tissue of the thigh, neck, cheek, and leg, and in the periosteum. Specific types are the multiple myxomas of the peripheral nerves, the myxoma of the umbilical cord, and the myxoma of mucous membranes.

Mixed Types. Many myxomas are not pure—fibromyxoma, lipomyxoma, fibrolipomyxoma, and chondromyxoma. These are most frequently seen in the retroperitoneal tissue, in the mediastinum, about the hilum of the kidney, and in the leg.

Related Lesions. *Polypoid Tumors of the Heart.* On rare occasions smooth, pedunculated, gray, translucent tumors are observed in the heart, most frequently on the atrial septum. They consist of an edematous or myx-

omatous, loose, connective tissue, with foci of hemorrhage and perivascular infiltration. On the surface there is usually organization of a superficial thrombus, and it seems probable that the entire mass is an organized thrombus and not a true neoplasm.

Clinicopathologic Correlation. The myxoma is a slow-growing tumor with considerable invasive capacity, so that recurrence after removal is common.

and the surrounding tissue. The microscopic structure resembles that of normal fat tissue. Between the fat cells there is a variable amount of stroma, and in some areas there are embryonal fat cells, polyhedral or round, with central nuclei and a finely vacuolated cytoplasm. Vascular channels are abundant. Secondary changes include myxomatous degeneration, cyst formation, hemorrhage, and calcification.

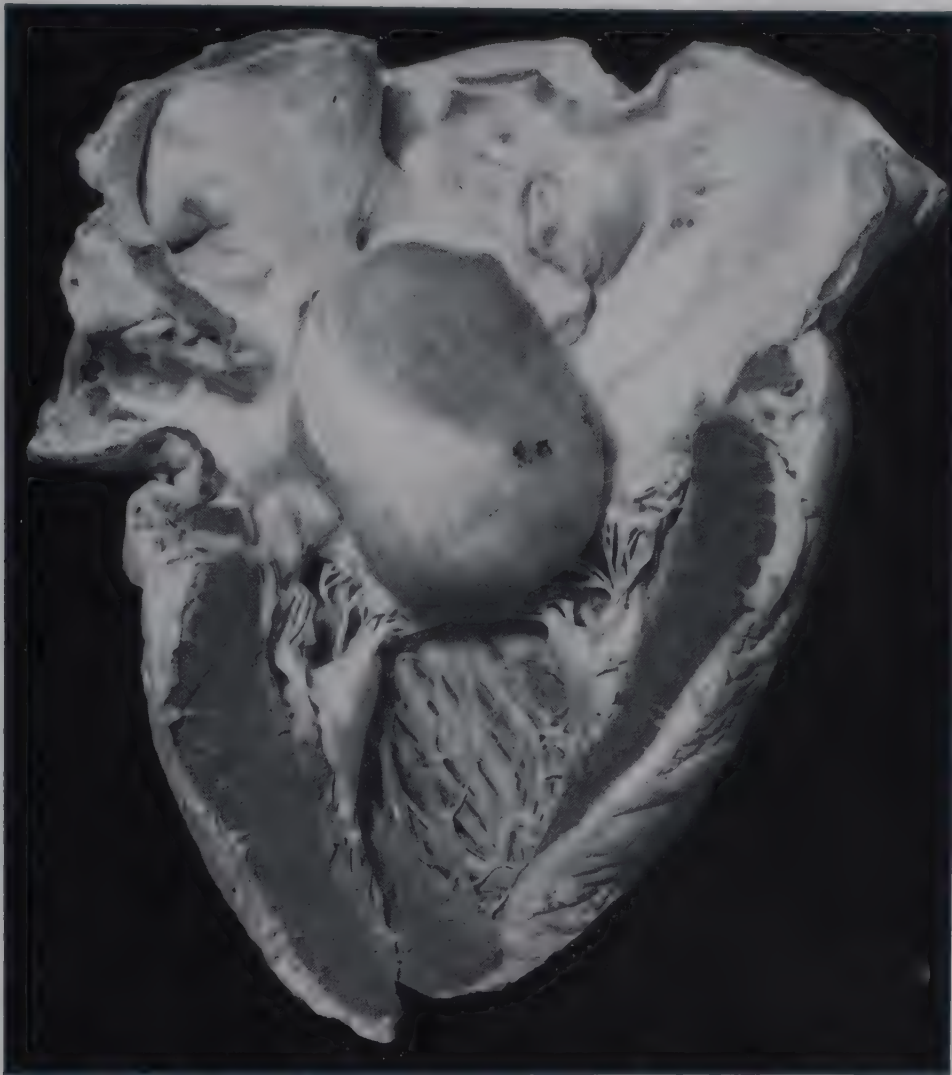


Fig. 82. So-called "myxoma" of heart. (Photograph by courtesy of Prof. C. H. Hu.)

Myxosarcoma. Because of the invasion seen in many otherwise benign myxomas the diagnosis of myxosarcoma must rest on microscopic observation of numerous mitoses and on a high degree of cellularity.

Tumors of Fat Tissue—Lipoma; Liposarcoma

Pathologic Anatomy. The lipoma is characteristically a firm, elastic, spherical, multilobulated tumor, circumscribed but not encapsulated, yellow and translucent. Each lobule of the tumor is supplied by a branch of the main blood vessel, and there is little anastomosis between lobules, and between tumor

Incidence. Clinical Types and Distribution.

The lipoma constitutes from 4 to 5 per cent of all benign tumors. The highest incidence is in adult life from twenty to fifty years. Several clinical and anatomic types of lipoma are recognized—subcutaneous, intermuscular, synovial, intracranial, interscapular, and visceral. The subcutaneous lipomas are the most common. They are found on the trunk and on the upper part of the extremities. The intermuscular type is seen almost exclusively between and in the muscles of the upper arm and thigh (Behrend). Specialized types are found in the diaphragm (Ballon and Spector) and in the tongue (Halpert). The synovial lipoma is a lobulated or papillary mass of fat

covered by synovia projecting into the cavity of the joint, and is probably not a true tumor. Lipomas of the central nervous system are most commonly located on the dorsal surface of the corpus callosum, in the region of the tuber cinereum, the mammillary bodies, and midbrain, in the choroid plexus, and in the leptomeninges of the brain stem and of the cord. They are associated with other congenital anomalies, particularly spina bifida. They should be distinguished from the lipomatous types of meningioma of Cushing.

The more important visceral lipomas are in the retroperitoneal or perirenal tissues, mesentery, omentum, mediastinum, tunica vaginalis (Senger and Bottone), and certain hollow and solid viscera. They are more common in women from forty to sixty years of age, and may give symptoms of obstruction. Small hamartomatous nodules of fat seen in the cortex and pyramids of the kidneys occasionally represent true lipomas (Robertson and Hand). Certain lipomas of the neck and of the interscapular region are brown and firm, and show microscopically a structure similar to that of fetal fat. It is believed by some that these represent a separate type of lipoma derived from the so-called "fat glands" (Inglis).

Pathogenesis. It is not possible to decide whether the lipoma in an adult is derived from normal adult fat tissue, from remnants of fetal fat, or from perivascular undifferentiated mesenchymal cells.

Causal Factors. Some lipomas follow the distribution of blood vessels, while others are arranged along the course of nerves or are associated with neurofibromas, suggesting an important causal role for vascular supply and nerve supply. Heredity is a factor only in the multiple tumors.

Clinicopathologic Correlation. Most lipomas produce no symptoms and come to the attention of the patient only because of the presence of a mass. The tumor is attached to the skin by small fibrous trabeculae, and hence shows the characteristic pigskin appearance on pressure. With increase in the size of the tumor, important blood vessels, nerves, and hollow viscera may be impinged upon. Ulceration and secondary inflammation may produce pain. Fat transilluminates and is radiolucent—two properties which may be used in establishing the diagnosis.

Related Lesions. The lipoma should not be

confused with localized hyperplasia of fat, with fat infiltration or lipomatoid replacement, with fibromas that have undergone fatty change and have the appearance of xanthomas, with the xanthomatous deposits in lipoid histiocytosis, or with the abnormal localized deposits of fat seen in patients with disease of the endocrine glands, all of which conditions are discussed elsewhere.

Liposarcoma. The malignant tumor of fat cells is most frequently seen in the intermuscular tissue of the buttocks and lower extremities and in the retroperitoneal tissue. The tumor is usually soft, and gray or yellowish gray. The cells are large and coarsely or finely vacuolated. The nuclei are relatively large and hyperchromatic (Ackerman and Wheeler; Stout).

Tumors of Vessels—Angioma; Endothelioma

Benign tumors of vessels are of two types, hemangioma and lymphangioma. Most examples are not autonomous neoplasms but remnants of fetal tissue misplaced or disordered in development; in other words, hamartomas or choristomas (Stout).

Hemangioma. Two types of benign tumors of blood vessels may be recognized: hamartomatous hemangioma, and hemangioblastoma.

Hamartomatous Hemangioma. PATHOGENESIS. If during development a small mass of vascular tissue is misplaced or distorted, it may persist as a tumor. With growth of the body the mass will grow and become evident. Because of stagnation of blood, trauma, or other factors, new vessels may form and enlarge the total mass more rapidly than the body as a whole grows.

TYPES. It is customary to recognize two types, capillary and cavernous. Capillary hemangiomas, composed of numerous small capillaries separated by a moderately cellular connective tissue, are most commonly seen on the skin of the face, and are known as "simple hemangiomas." Cavernous hemangiomas composed of widely dilated channels, separated by connective tissue trabeculae, are most frequently seen in muscle, in bone, and in the liver (Geschickter).

HEMANGIOMA OF THE SKIN. Both the capillary and cavernous types are seen in the skin. The sites of predilection in order are face,

extremities, back, lip, scalp, chest, and abdomen. Most are present at birth and grow steadily with the body. Occasionally either type may acquire neoplastic properties, invade, and grow rapidly as the angioblastic type.

HEMANGIOMA OF MUSCLE. Hemangiomas of muscle are usually cavernous, and occur in order of frequency in the muscles of the lower extremities, trunk, and upper extremities. Calcification of a thrombus is frequent

up of numerous cavities filled with blood. The vascular spaces are lined by endothelium, and separated from one another by narrow or broad connective tissue trabeculae. Within the connective tissue trabeculae, especially near the edge, small bile ducts and branches of the portal or hepatic system may be seen. Occasionally, the vascular spaces are replaced by thrombi in all stages of organization.

It has long been assumed that these tumors are hamartomas. A number of observations

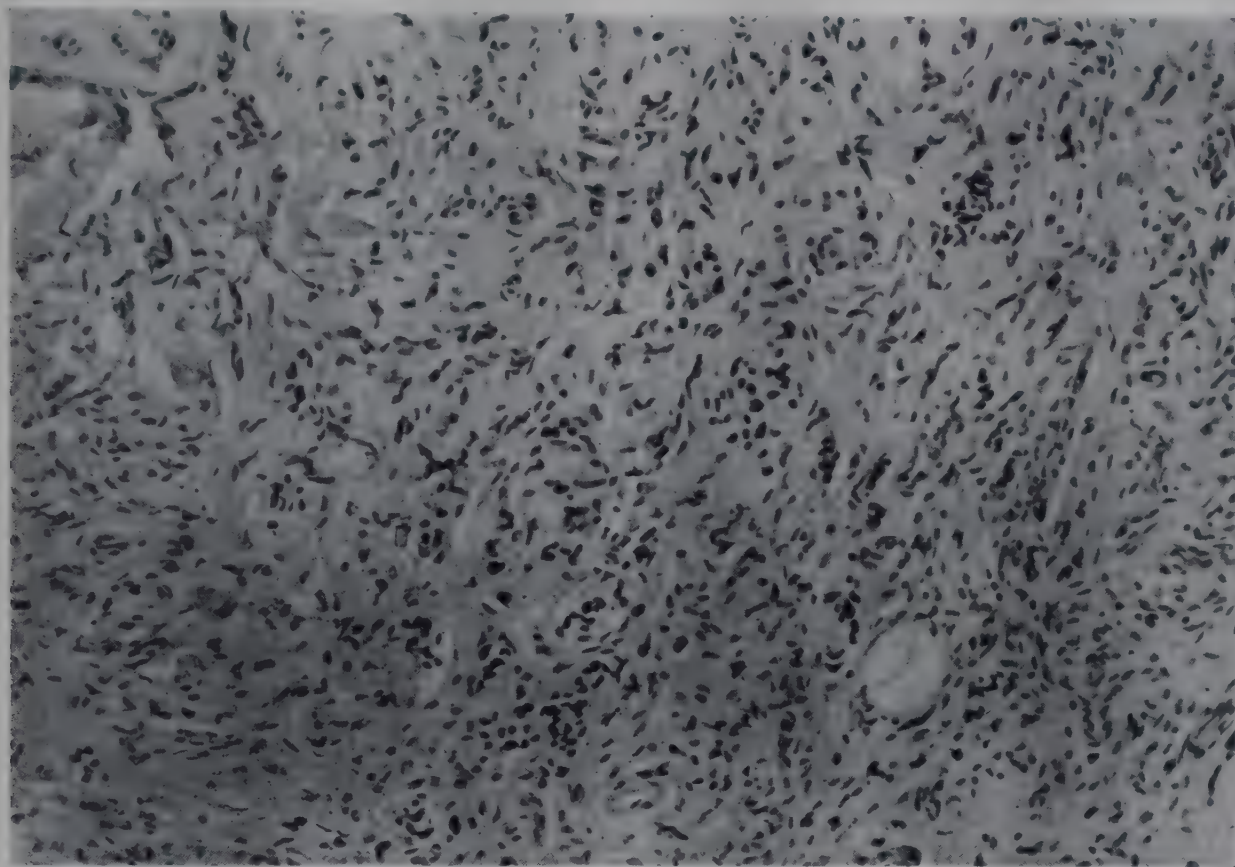


Fig. 83. So-called "sclerosing hemangioma" or "subepidermal fibrosis."

and constitutes a valuable diagnostic sign. Many are present at birth, and trauma, either external or internal, from movement of the muscles constitutes the stimulus for growth. There is gradual invasion of the aponeuroses and surrounding muscles (Davis and Kitlowski).

HEMANGIOMA OF BONE. Careful examination of the vertebral bodies at autopsy reveals small cavernous hemangiomas in about 10 per cent of all persons (Topfer). Similar tumors in other bones, notably the skull, have been observed. The bone is expanded locally, and the sinusoids ramify through the irregular trabeculae to give a loculated appearance (Bucy and Capp).

HEMANGIOMA OF THE LIVER. The usual hemangioma of the liver is a small, red, spherical or pyramidal mass, 3 to 10 mm. in diameter, just beneath the capsule of the liver, made

indicate however that this is not correct. Hemangiomas of the liver are rarely observed in children, and become progressively more frequent with increasing age. They are observed in women more frequently than in men in a ratio of about 6:1. A far more logical hypothesis is that hemangioma of the liver is an acquired lesion resulting from destruction and necrosis of all of the liver cells in a focal region. Similar lesions are occasionally seen in the spleen.

HEMANGIOMA OF THE NERVOUS SYSTEM. Congenital anomalies in the formation of vessels of the brain, retina, or spinal cord may result in a focal mass of sinusoidal spaces. When all are present, together with anomalies of the kidney, liver, and pancreas, it constitutes Lindau's disease (full discussion, p. 953).

Hemangioblastoma. In certain hemangi-

omas there is conspicuous proliferation of endothelial cells, filling the vascular spaces, and occasionally invading the surrounding tissue. They undoubtedly represent a true benign neoplasm of endothelium.

Related Lesions. SPIDER TELANGIECTASIS. In older persons, in pregnant women, and in patients with chronic hepatic disease or with nutritional deficiencies, small foci of radiating or interlacing vessels may appear in the dermis, sometimes associated with other vascular phenomena. It has been suggested that these are basically related to a disturbance in the metabolism of 17-ketosteroids (Bean).

FOCAL TELANGIECTASES OF THE INTESTINAL MUCOSA. Small, sessile masses of dilated veins, 1 to 5 mm. in diameter, are occasionally seen in the intestinal mucosa. It is probable that both congenital and acquired varieties exist.

SCLEROSING HEMANGIOMA. Gross and Wolbach have described under this name a lesion which others consider to be a reactive fibrosis.

Lymphangioma. If a strict definition is applied: "an isolated autonomous growth of lymph vessels disconnected from surrounding channels," there are probably a few true lymphangiomas.

Specific lesions usually called "lymphangiomas" include circumscript lymphangioma of the skin, multiple tuberous lymphangioma of the skin, cavernous hemangioma of the skin, chylangioma of the mesentery arising from congenital or acquired obstruction of the lacteals, and lymphangioma of the retroperitoneal, mesenteric, and sacral regions.

Three anatomic types are recognized: simple, cavernous, and cystic. The simple lymphangioma consists of anastomosing small and medium-sized vessels, separated by thin trabeculae of connective tissue. The endothelium is flat or cuboidal, and rarely shows proliferation. The cavernous lymphangioma is a system of closed communicating spaces, separated by thick septa and lined by endothelium. The cystic lymphangioma consists of small and large cysts, lined by flat endothelium and filled with lymph (see p. 800).

Endothelioma. Many tumors of manifestly separate cellular types have at one time or another been grouped as "endotheliomas." Ewing summarizes the facts in the following words:

"Although there have been numerous attempts to establish differential diagnostic signs

between endothelioma and other tumors, it must be admitted with Lubarsch that reliable criteria of general application are lacking. . .

"The most reliable sign of endothelioma is found in the minute characters of the cells as above described, but these characters are lost in many actively growing tumors, and in recurrences. Yet a thorough search for the translucent polyhedral cells, with pale nuclei devoid of acidophile nucleoli, is often rewarded in tumors, the bulk of which fails to show such cell types. Especially in edematous foci the pavement characters reassert themselves."

Perithelioma. Occasionally tumors are observed in which numerous arterioles are each contained in a sheath of polygonal, rounded, or stellate cells, radiating from the vessel. Between these roughly circular masses the tissue is edematous, hemorrhagic, or necrotic. In the belief that this represents a distinct histogenic type, some use the term "perithelioma" or "periendothelioma."

A tumor derived from the pericytes (probably modified smooth muscle) has been described under the name of hemangiopericytoma (Stout and Murray).

Tumors of Hematopoietic Tissues— Lymphoma; Myeloma; Lympho- sarcoma; Leukemia

Malignant tumorous conditions of the hematopoietic tissues are all definite disease entities, and are discussed in other chapters.

Lymphoma. A clear delineation of a benign tumor of lymphocytes from inflammatory hyperplasia presents great difficulties. In an occasional patient focal enlargement of the lymph nodes, which are firm and composed of grayish white tissue, is observed. There may be diffuse hyperplasia of small lymphocytes or prominent primary follicles. The reports of an apparent cure of lymphosarcoma by surgical excision of a regional group of nodes (Gall and Mallory; Stout) may mean that we have not yet established the criteria for the histologic distinction between lymphoma and lymphosarcoma.

Tumors of Muscle—Myoma; Myosarcoma

During early development the mesoderm spreads out to form definite parts of the supporting tissues. For purposes of classification

of the myomas the mesoderm may be divided into four categories: that applied to the body wall, that applied to the digestive tract and vascular system, a paraxial mass, and an intermediate cell mass.

From a histologic standpoint four different types of tumors of muscle are recognized: leiomyoma, leiomyosarcoma, rhabdomyoma, and rhabdomyosarcoma.

Leiomyoma. *Pathologic Anatomy.* The leiomyoma is an encapsulated, firm, spherical tumor. When sectioned, the capsule and the surrounding tissue retract, revealing a grayish white, glistening cut surface, with irregular

LEIOMYOMA OF THE UTERUS. Leiomyomas, or "fibroids," of the uterus are usually multiple, and may be subserous, intramuscular, or sub-endometrial. In the first and last, pedunculation is the rule. Similar tumors arise in the broad ligament (full discussion, p. 908).

LEIOMYOMA OF THE GASTRO-INTESTINAL TRACT. Small, single leiomyomas, 5 to 15 mm. in diameter, are seen in the wall of the esophagus, stomach, and small intestine. They are rarely of any clinical importance.

Mixed Types. The adenomyoma of the uterus is the best example of a mixed myoma. The endometrial glands are surrounded by



Fig. 84. Leiomyoma.

interlacing bundles of "watered silk." Foci of necrosis, cyst formation, fibrosis, and calcification are common in the larger tumors. The cells are spindle-shaped, and are arranged in parallel bands or whorls. Myoglia can be demonstrated with special stains. Vascularization in general is poor.

Incidence. Clinical Types. Distribution. This benign tumor of smooth muscle is one of the most common tumors of the human being. Thus in a ten-year experience at the Memorial Hospital, leiomyomas of the uterus made up 4.21 per cent of all admissions and 39 per cent of all benign tumors. This tumor was exceeded in frequency only by squamous cell and basal cell carcinoma of the skin, carcinoma of the cervix, and carcinoma of the breast—all malignant tumors.

typical endometrial stroma and joined by the neoplastic muscle. The adenomyoma should not be confused with non-neoplastic heterotopic endometrium—endometriosis (full discussion, p. 907).

Causal Factors. There are no known causal factors of leiomyomas except of leiomyoma of the uterus, in which constitution, hormones, and maldevelopment appear to be active. The influence of constitution is reflected in a high incidence in Negro women. The importance of hormones is emphasized by the rarity before puberty and the peak incidence towards the end of sexual life. The factor of disturbed development is supported by the finding of heterotopic inclusions in some myomas.

Clinicopathologic Correlation. In hollow viscera, myomas may produce obstruction. A

subendometrial myoma usually ulcerates, and there is uterine bleeding.

Rhabdomyoma. All tumors of striated muscle are rare. In many mixed tumors, especially those about the kidney, striated muscle cells are a component.

Pathologic Anatomy. The benign tumor of striated muscle, rhabdomyoma, is a large, reddish gray, soft, encapsulated or infiltrating mass. The characteristic cell is large, with many protoplasmic processes, at times forming a syncytium. The cytoplasm is richly vacuolated, and in the processes there are definite granules, arranged in longitudinal and cross-

grow rapidly and form large, soft, gray masses.

Mixed Forms. In addition to definite types of mixed tumors containing striated muscle, a teratoma of the testis or ovary may have a one-sided development as a rhabdomyoma.

NEPHROMA (ADENOSARCOMA, WILMS' TUMOR). This is a neoplastic type found in the kidney and retroperitoneal tissues, which reproduces in whole or in part the derivatives of the somites in the nephrogenic region (full discussion, p. 791).

RHABDOMYOMA OF THE UTERUS (BOTRYOID SARCOMA). In the vagina of children and in

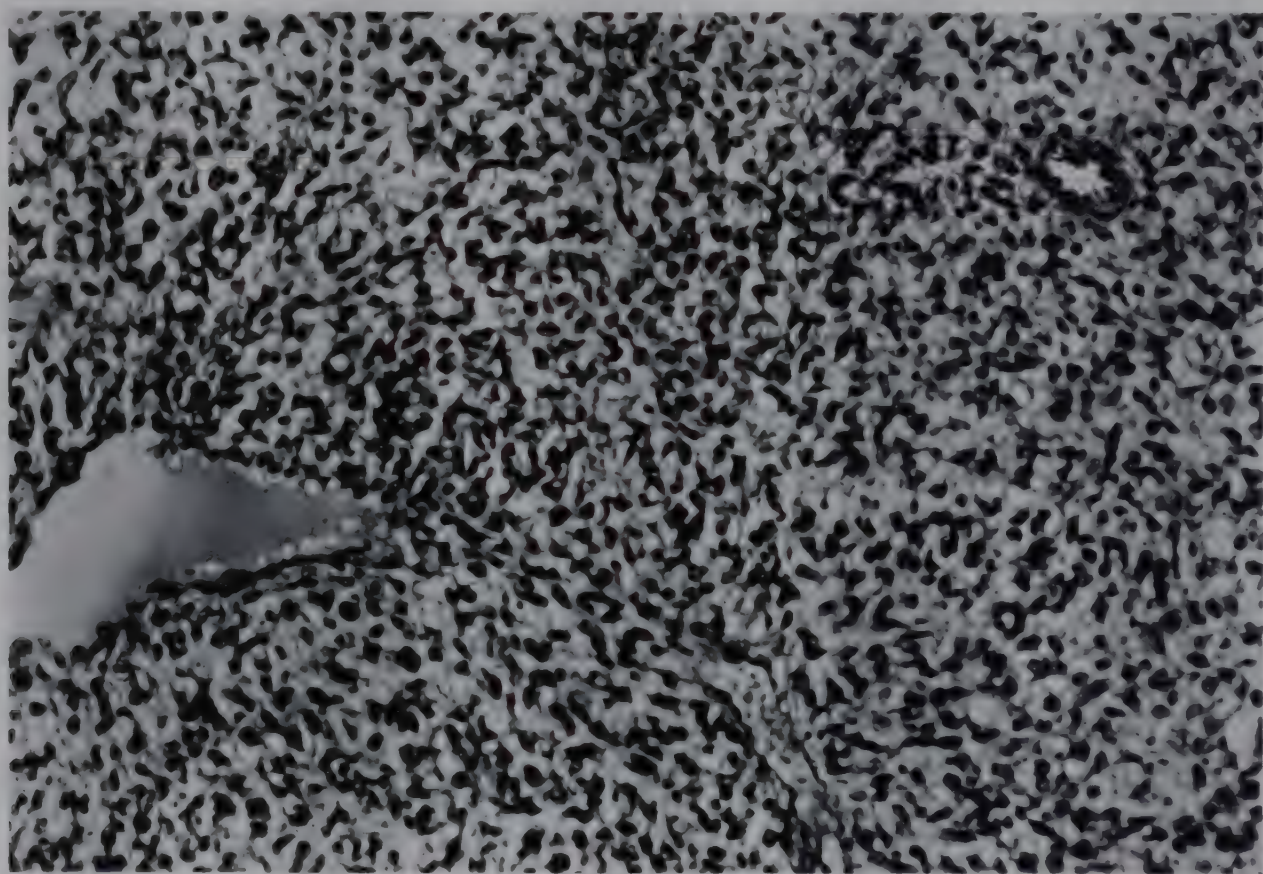


Fig. 85. Rhabdomyosarcoma.

striations. Multiple nuclei are common. A definite sarcolemma may be present.

Incidence. Types. The most common sites are the heart and the genito-urinary organs, but any region with muscle may be the point of origin.

RHABDOMYOMA OF THE HEART. Rhabdomyoma of the heart may occur as an isolated tumor or as a part of an anatomic complex consisting of tuberous sclerosis, sebaceous adenoma of the face, anomalies of the kidneys, and tumors of the heart. Many are congenital, and few patients live over three years.

RHABDOMYOMA OF THE GENITO-URINARY SYSTEM. Rhabdomyomas of the kidney, of the bladder, and of the prostate have been described. Most are in children, and the tumors

the cervix and fundus of adults there is a tumor composed largely of spindle cells, islands of cartilage, and a few striated muscle cells (full discussion, p. 912).

Leiomyosarcoma. Leiomyosarcomas are soft, gray or reddish gray, fleshy tumors, seen most frequently in the uterus and gastro-intestinal tract. The cells are closely packed and spindle-shaped, and have blunt-ended nuclei. Mitoses are abundant, and tumor giant cells are generally observed. The stroma is scanty. In uterine myomas, sarcomatous foci are found in about 1 per cent.

Rhabdomyosarcoma. The distinction between a benign and a malignant tumor of striated muscle is not always easy to make. Many embryonal tumors with numerous multinucle-

ated cells and a striated cytoplasm have been designated "sarcomas." They are bulky, gray, and invasive. Recurrence is the rule, but metastases do not always appear (Stout).

Tumors of Mesothelium— Mesothelioma

Tumors derived from the mesothelial cells of the peritoneum, pleura, and pericardium are exceedingly rare if they exist at all (Wil-
lis).

Tumors of the pleura are of two types, local and diffuse. The lung is encased in a layer of white, firm tissue, 1 to 2 cm. in thickness. The cells are polygonal, and are arranged in cords and sheets and separated by dense connective tissue. The type cell has an abundant cytoplasm and a large, vesicular nucleus with finely divided chromatin, an irregularly infolded nucleus, and prominent nucleoli. Occasionally the cells are definitely epithelial and form papillae projecting into the pleural cavity (Yoshida). Similar tumors of the pericardium and peritoneum have been described.

Malignant Tumors of Mesoderm— Sarcoma

The malignant tumors of mesoderm may be classified histogenetically or cytologically. The histogenetic classification is to be preferred, and each type has been discussed in preceding paragraphs—fibrosarcoma, myxosarcoma, etc. Since the behavior of a tumor and the prognosis for the patient depend on the biologic potentialities of the cell and not on its shape, it seems well to abandon the cytologic classification entirely (Stout).

Benign Tumors of Covering Epithelium —Papilloma; Polyp

In the histogenetic sense a papilloma is a local outgrowth of lining cells and the underlying connective tissue. For clarity the use of the word to describe gross appearance should be abandoned. The term "polyp" has been employed to designate any sessile or pedunculated, smooth-surfaced, local overgrowth of tissue, whether inflammatory or neoplastic, regardless of the cytologic components. Exactness of diagnosis necessitates the use of a modifying adjective such as "adenomatous" or "lipomatous" (Helwig).

Papillary overgrowths of epithelium in man may be divided into three classes: those

caused by micro-organisms, those of unknown or obscure cause involving the skin, and those of unknown or obscure cause involving an internal viscus. Each of these is fully discussed in other chapters. The cutaneous types of infectious or of obscure cause are discussed in the chapter on diseases of the skin (p. 1006). The more important varieties derived from epithelium of the hollow viscera are papilloma of the larynx (p. 684), and papilloma of the urinary tract (p. 783). In all, multiple tumors are common, and there are many facts that suggest a viral cause and a relation to hormones.

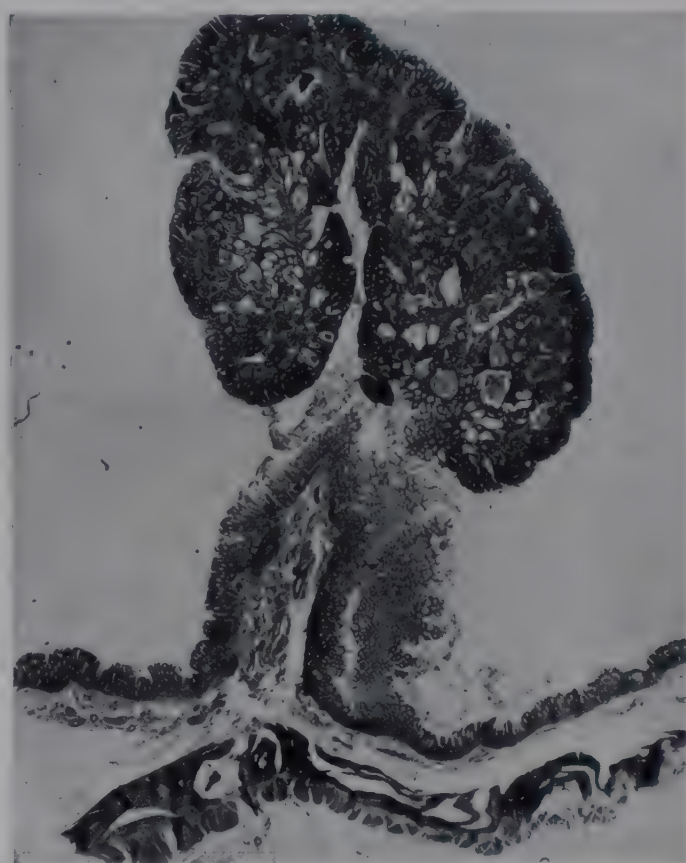


Fig. 86. Polyp of the colon.

General Pathologic Anatomy. Each papilla is covered by hyperplastic epithelium and supported on a loose, well vascularized connective tissue. Secondary changes include metaplasia, hyperkeratosis, ulceration, and inflammation.

Transformation to Carcinoma. Some papillary overgrowths and papillomas rarely if ever transform into carcinoma, while others are definite "precancerous" lesions. In the latter group are senile keratoses and papillomas of the bladder and larynx.

Benign Tumors of Glandular Epithelium—Adenoma

An adenoma is a benign, organoid tumor which reproduces the structure of the gland.

Pathologic Anatomy. The adenoma is a well circumscribed and encapsulated tumor, showing no invasion of the surrounding tissue, and is easily shelled out after incision of the capsule. Two types are recognized: tubular adenoma and cystic adenoma.

Tubular Adenoma. The tubular adenoma is composed of relatively solid, firm tissue, consisting of two parts: small, solid or cleftlike, light yellow dots and streaks, less than 1 mm. in diameter, and a grayish white fibrillar supporting tissue. The dots and streaks are the epithelial acini, round or irregular, and lined by a single or multiple layer of cells. Occasionally, small papillomas project into the lumen. In some tumors, notably in the breast, the connective tissue appears to be neoplastic, and these are designated as "fibro-adenomas" (full discussion, p. 915).

Cystic Adenoma. Regularly in some organs (the ovary) and occasionally in other organs (the breast) the most prominent macroscopic feature of an adenoma is one or more cystic spaces filled with fluid. The lining of the cysts may be smooth, or there may be numerous papillomas projecting into the lumen. The best examples are the serous and the pseudomucinous cystadenomas of the ovary (full discussion, p. 886).

Malignant Adenoma. In certain organs, chiefly the thyroid, there are tumors that have an alveolar structure with definite arrangement and normal polarity of the cells, but lack a limiting membrane of connective tissue. The stroma is sparse, and the acini are closely packed. Careful examination will reveal invasion of blood or lymph vessels. Here then is a tumor that has a low degree of anaplasia, that has invasive properties, and that produces metastases. In order to distinguish it on the one hand from adenoma and on the other hand from carcinoma, the term "malignant adenoma" seems most suitable.

Transformation to Carcinoma. Adenomatous polyps of the colon are a common forerunner of carcinoma, and papillary cystadenoma of the ovary not infrequently becomes a cystadenocarcinoma by invasion of the capsule. On the other hand, fibro-adenoma of the breast only occasionally becomes a carcinoma or a sarcoma.

Related Lesions. Focal Hyperplasia. In many organs, notably those tissues under endocrine control, localized collections of hyperplastic cells in the form of nodule are fre-

quently seen. The cells are oriented, reproduce the architecture of the organ, and are separated from the surrounding tissue only by compressed parenchyma. The most satisfactory explanation of focal hyperplasia is repeated stimulation and involution, with isolation of a group of cells which are more responsive to the stimulus and involute less on withdrawal (Rienhoff). Similar focal hyperplasias in the kidney and liver are apparently related to regeneration after injury, and are frequently multiple.

General Considerations of Carcinoma

A carcinoma is a malignant tumor composed of anaplastic epithelial cells. The term thus encompasses tumors of ectoderm, endoderm, and specialized mesodermal derivatives.

Qualities common to all carcinomas at some stage in their evolution are anaplasia of cells, lack of orientation and polarity of cells, invasive growth, invasion of lymphatic vessels and to a less extent of blood vessels, ulceration through the surface, and formation of distant metastases.

Epidermoid Carcinoma

Epidermoid carcinoma may originate in any organ or tissue with epithelium, but is most common in those normally containing squamous epithelium, such as the skin, buccal cavity, esophagus, and cervix.

In the skin there are two important types of carcinoma, one reproducing the keratinized parts of the epidermis (epidermoid carcinoma), and the other reproducing the structure of the basal cells or the cells of the hair follicles (basal cell carcinoma).

Epidermoid Carcinoma. Epidermoid carcinoma (squamous cell carcinoma, epithelioma, acanthoma) has a similar structure, regardless of the organ of origin. The first recognizable lesion is either an elevated papillary growth or an indurated, infiltrating nodule beneath the surface, in which central ulceration develops. On section of a well developed tumor, small, round paper-white islands, embedded in the gray stroma, are readily seen. The characteristic feature observable microscopically is the epithelial pearl, a concentrically laminated structure with epidermal cells on the outside, fully keratinized cells on the inside, and gradations in the intermediate zone. Between some cells intercellular bridges are present. The nuclei vary greatly in size and chro-

matism. Multinucleated cells are common, and there are distinct large nucleoli. The cells may become spindle-shaped in the most anaplastic tumors, and the distinction from sar-

ulcerates onto the surface. The ulcer is ragged, has a dirty, irregular base, and an indurated, elevated edge. The typical polygonal or spindle-shaped chromatic cells are arranged in



Fig. 87. Epidermoid carcinoma. (Photograph by courtesy of Dr. Zola Cooper.)

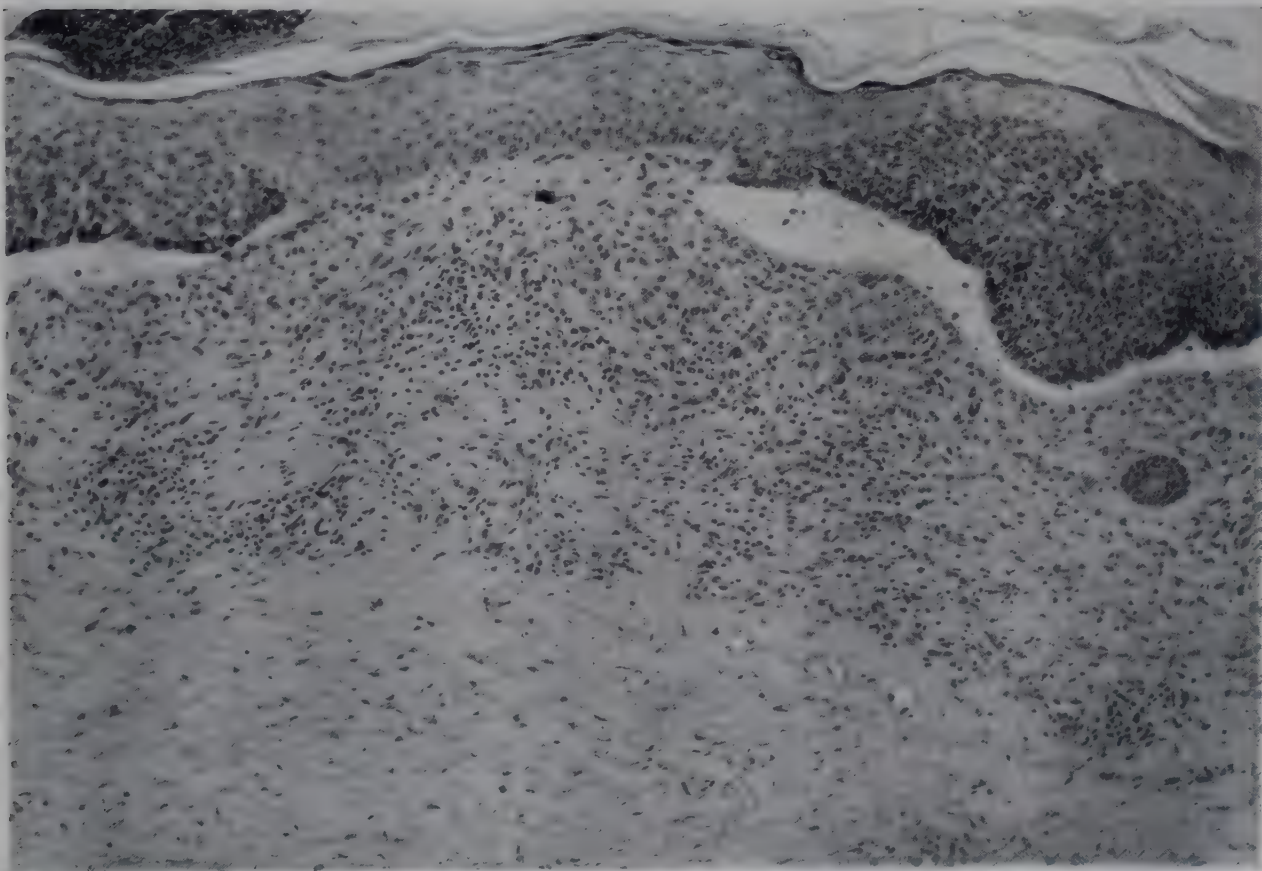


Fig. 88. Basal cell carcinoma. (Photograph by courtesy of Dr. Zola Cooper.)

coma requires careful study (full discussion, p. 1016).

Basal Cell Carcinomas. The basal cell carcinoma (rodent ulcer) begins as a small nodule in the dermis, slowly enlarges, and finally

isolated or intercommunicating cords and masses. The peripheral cells of each cord are oriented and cuboidal (full discussion, p. 1014).

Adeno-acanthoma. A mixture of adenocar-

cinoma and epidermoid carcinoma is seen in the cervix and occasionally in the uterine fundus.

Transitional Cell Carcinoma

In the nasopharynx and in the urinary tract there are epithelial tumors, solid or papillary, in which the cells lining the lumen are characteristically polygonal and multilayered, but do not show any tendency to keratinization, and do not show intercellular bridges. In the nasopharynx they are large, bulky, reddish gray, friable tumors, growing into the lumen

(the breast) and of a typical carcinoma of a hollow viscus (the colon).

Carcinoma of Breast. At the time when most women with a possible carcinoma of the breast come to the physician, the tumor is a single, firm, irregularly outlined nodule, which can be moved about in the softer surrounding tissue only to a limited degree. On the cut section a firm, opaque, grayish-white, irregular mass, with fine, radiating strands about the periphery, is seen. Within a gray or white fibrillar, semitranslucent tissue small, yellow, softer, slightly elevated islands are discernible. On scraping, a fluid with suspended chalky

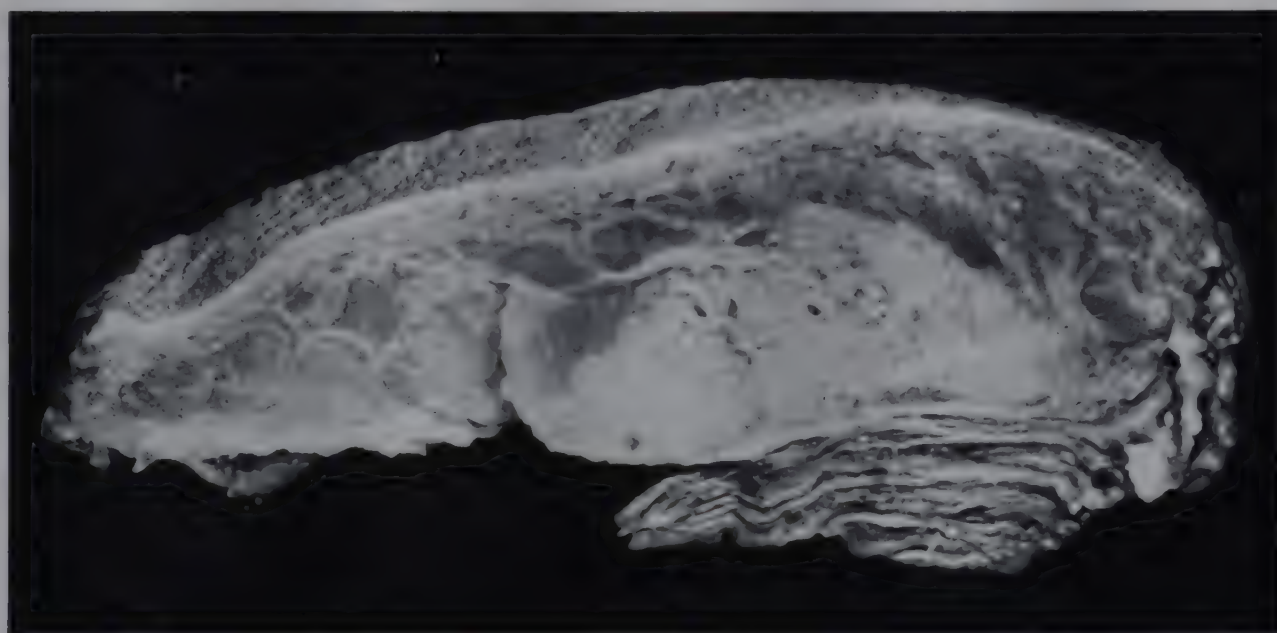


Fig. 89. Carcinoma of the breast.

and obstructing the principal air passages and the orifices of the accessory nasal sinuses and the eustachian tube (full discussion, p. 642). In the urinary tract the characteristic structure is papillary, and multiple tumors are the rule (full discussion, p. 783).

Lympho-epithelioma. The lympho-epithelioma is a special type of transitional cell carcinoma in which there is an admixture of sheets of large, polygonal, pale, epithelial cells and small lymphocytes, both in the primary tumor in the nasopharynx, and in the metastases. It is extremely radio-sensitive (full discussion, p. 642).

Cylindrical Cell Carcinoma

Cylindrical cell carcinoma constitutes the great mass of malignant epithelial tumors.

Pathologic Anatomy. The appearance of the carcinoma varies with the tissue of origin and the structure, but a composite description follows of a typical carcinoma in a solid tissue

white or yellow particles can be secured. With continued growth the primary mass becomes larger, the radiating strands into the adjacent fibro-adipose tissue are more prominent, and the suspensory ligaments to the skin appear as broad, gray, firm trabeculae. If the tumor reaches the surface, there is likely to be ulceration.

Carcinoma of Colon. Specimens of carcinoma of the colon are rarely seen by the pathologist until they have reached a relatively large size and caused stenosis of the lumen. For a distance of 5 to 15 cm. the wall of the colon is firm. The peritoneum is slightly thickened and opaque. The small, subserosal lymphatics are prominent, and consist of white, firm, interlacing lines. On opening the intestine, a fungating, ulcerated, papillary mass of gray or grayish pink, friable tissue is seen. The lumen is small or completely occluded. The distinct layers of the intestinal wall are interrupted in the region of the tumor, and the pearly gray, firm muscularis is infil-

trated by white tissue, or is completely destroyed.

Types. The following varieties of carcinoma are worthy of differentiation and separate consideration.

Carcinoma in Situ. The cells are atypical, and completely fill an acinus. At no point, however, is there any interruption in the basement membrane.

Adenocarcinoma. The cells retain their polarity and line definite acini.

Comedocarcinoma. In some organs the adenocarcinoma is composed of small, duct-like acini, and the lumens are filled with inspissated secretion. This type is known as "comedocarcinoma." In general the comedocarcinoma is somewhat less malignant than the usual adenocarcinoma.

Mucinous Carcinoma. There are two distinct types of carcinomas in which the cells elaborate large amounts of mucin. One is an adenocarcinoma, and the mucin is secreted into the acini, which become greatly distended. In the other the mucin is retained within each neoplastic cell as a large vacuole. The nucleus is pushed to one side, and the structure is that of a signet-ring cell. The two are separated because the former is less malignant than the latter.

Carcinoma Simplex. In the carcinoma simplex, which includes most of the undifferentiated types of carcinoma, there is no polarity, and the cells are arranged in irregular cords and sheets, separated from one another by narrow or broad bands of connective tissue.

Scirrhou carcinoma. In an occasional carcinoma simplex there is a growth of dense connective tissue, and the neoplastic cells are sparse. This is designated as "scirrhou carcinoma."

Mixed Tumors

In certain parts of the embryo—the metanephrogenic ridge and the neck about the salivary gland—mesoderm differentiates into epithelium, or epithelium shells off the ectoderm and is transformed into mesodermal cells. Thus there are in these two locations cells with multiple but limited potentialities to form tumors composed of both epithelial and connective tissue elements, that is, true mixed tumors. A full discussion of mixed tumors of the salivary gland type is given on page 643, and of the embryonal nephromas on page 791.

Teratoid Tumors

In contrast with mixed tumors which have limited capacity of differentiation, the teratoid tumors may include all tissues found in the embryonic and adult body. They occur in the gonads, retroperitoneal tissues, mediastinum, and region of the pineal. Many contain trophoblastic cells as well as somatic (see full discussion under tumors of the testis, on p. 892).

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PART II

DISEASES CAUSED BY LIVING AGENTS



XIV

The Infectious Diseases: General Considerations

The infectious, contagious, or communicable diseases constitute a group which have in common the fact that a living agent—bacterium, virus, rickettsia, protozoan, or metazoan—is the cause. The nature of the disease produced is the result of an interplay between the invading parasite and the invaded host. Many of the factors which are basic to this interplay are common to all the infectious diseases and will be discussed in this chapter.

Toxemia Versus Infection

With the infectious diseases it is possible to arrange a scale, at one end of which are pure toxemias and at the other end overwhelming invasive infections. In pure toxemias, represented by food poisoning, the bacteria grow outside the body in food and produce a toxin which when ingested is absorbed and causes disease. The bacteria may be entirely innocuous and incapable of producing any disease when ingested without preformed toxin, or they may invade the body and produce an infection as well as a toxemia. Tetanus is one step up the scale. The bacteria are introduced into the superficial tissues of the body, grow at that point, produce little or no inflammatory reaction, but form large amounts of toxin which is absorbed and is entirely responsible for the signs and symptoms. Diphtheria is the next step. The bacteria remain localized, but are responsible for a serious local inflammation. Toxin is absorbed and brings about changes in the internal viscera. It differs from tetanus in that occasionally the bacteria invade the body. Gas bacillus infections are a little farther along the scale, in that there is regularly a terminal invasion. The streptococcus combines the activities of both a toxigenic

organism and an invasive organism. It may grow in the pharynx and secrete a toxin which causes scarlet fever. On the other hand the bacteria may invade the blood and result in a true septicemia. Finally there is a group of bacteria of varying virulence that characteristically invade all the tissues of the body. Those of relatively low virulence are the treponema of syphilis and the leprosy bacillus, while those of high virulence are the bacterium of plague and of the hemorrhagic septicemias of animals.

Tissue and Cellular Localization

The tissues or cells attacked by any given disease-producing agent depend on a number of factors, notably, method of transmission, specific interrelations of tissue or cell and parasite, and state of the tissue.

Method of Transmission. The preponderant occurrence of syphilis and gonorrhea as venereal diseases is an expression of the method of transmission. Yet, when the treponema is inoculated on the skin at any point, as on the lips, a chancre results. Similarly the implantation of gonococci on the conjunctiva of the eyes of the newborn produces a purulent inflammation similar to that in the urethra.

The hemolytic streptococcus is in general transmitted from person to person as a droplet infection. The most common disease resulting therefrom is a pharyngitis. However, a pneumococcus transmitted in a similar way causes a inflammation of the lungs, and a meningococcus after reaching the pharynx as a droplet infection induces a mild local inflammation followed by a septicemia and meningitis.

It is apparent that method of transmission is an important factor, but not the only factor.

Specific Interrelations of Tissue or Cell and Parasite. A number of observations in man and in experimental animals indicate a specific interrelation of the tissue or cell involved and the parasite. For example, *Hemophilus pertussis* injected into the developing chick embryo localizes in the cilia of the air passages exactly as in man (Gallavan and Goodpasture). Hence, the airborne route of transmission of this bacterium has little to do with involvement of the respiratory tract. The virus of louping ill, regardless of the method of introduction into the body, localizes in the cerebellum and produces necrosis of the Purkinje cells (Rivers).

One of the best examples of tissue selectivity is the localization in rabbits of the Shope papilloma virus and the tongue papilloma virus. The former will produce papillomas on the skin about the mouth up to the vermilion border of the lip, while the latter will induce papilloma on the mucous membrane of the mouth up to the same point. Neither will cause papillomas in the tissue for which the other is selective (Parsons).

Although our information is only fragmentary it seems probable that selective localization is still the result of chemical interplay between cells and parasite. The production of a tubercle by the tubercle bacillus results from the liberation of protein, carbohydrates, and lipids by the bacillus and the ability of enzymes in the tissue to hydrolyze these substances, especially the lipids (Sabin).

State of the Tissues. If the only factors were the presence of disease-producing agents and susceptible tissue, the ubiquitous distribution of pathogenic bacteria and viruses would soon decimate man and animals. The protective covering of the body by epithelium and the normal defense mechanism prevent most disease. However, the general state of the tissue at the time is a factor. An alteration of the cells produced by one disease agent or condition will at times prepare the soil for others. The frequency of streptococcal pneumonia following viral diseases such as measles and influenza, and the low incidence of primary streptococcal pneumonia, is probably an example of this phenomenon. The greater incidence and severity of infections in older individuals may be related to fundamental changes in the tissue with age. In some instances, the broad concept of state of the tis-

sues can be more accurately stated. Colon bacilli in the blood stream in reasonable numbers will pass through a normal kidney without causing disease, but if there is an obstruction of the ureter the result is a pyelonephritis (Mallory, Crane, and Edwards). It is clear that obstruction produces some change in the kidney so that bacteria localize.

The Mechanism of Production of Disease

From what has been said about toxemia versus infection, and about tissue and cellular localization, it is apparent that whether or not disease results and what type of reaction is produced are the result of a composite of chemical factors in the host and in the parasite.

One of the best examples of the induction of disease by chemical substances is gonorrhea. Exactly the same reaction of the mucous membrane of the urethra results from living gonococci, dead gonococci, and lysed cultures of gonococci. There is thus within the gonococcus one or more chemical substances which cause a purulent inflammation.

Further delineation of the production of disease by chemical agents within bacteria is possible with the tubercle bacillus (Sabin). A pure substance, phthioic acid, isolated from tubercle bacilli will, when injected, cause formation of a typical tubercle, identical with that resulting from living tubercle bacilli. It would appear that in natural infection the lipids of the bacillus are hydrolyzed by enzymes of the host and phthioic acid is liberated. If this hydrolysis occurs slowly, disease results, but if it proceeds rapidly there is no lesion (Gerstt and Tennant).

Only a beginning has been made in exploration of this field of chemical interplay in disease. One toxin, the alpha toxin of *Clostridium welchii*, is known to be an enzyme of the lecithinase class (MacFarlane and Knight). It is possible that it injures or kills cells by splitting the lecithin and lecithoprotein of the protoplasm.

Many bacteria elaborate substances which are not directly toxic but which may influence the nature or course of disease. For example, some staphylococci produce a coagulase which accelerates the clotting of plasma. However, there is no evidence that this is a factor in the

characteristic form of staphylococcal lesions. On the other hand, the enzyme fibrinolysin secreted by many pathogenic streptococci may be responsible in part for the capacity of these organisms to spread through tissues.

An example of the chemical factors in the host is the possible relation of hyaluronic acid and hyaluronidase. The addition of a "spreading factor" such as an extract of testis to an inoculum of pathogenic bacteria results in a larger lesion than if it were not included. It has been postulated that "spreading factor"

the destruction of tissue. The condition is loosely spoken of as "toxemia."

Pathologic Anatomy. *Hyperplasia of Lymph Nodes.* The toxins absorbed by the lymphatics are carried to the regional lymph nodes and there cause a characteristic type of inflammation known as "hyperplasia of the lymph nodes." The lymph nodes are moderately enlarged. The capsule is tense. The structure is finely granular and pink, and bulges from beneath the capsule. The follicles are not grossly discernible. Microscopically, the sinusoids,



Fig. 90. Enlargement of the regional lymph node in a child with acute pharyngitis. (Photograph by courtesy of Dr. Theo. Walsh.)

is an enzyme hyaluronidase which hydrolyzes the ground substance of supporting tissue—hyaluronic acid—and thus permits spread (Duran-Reynals).

These few limited and tentative observations and interpretations indicate clearly the need for more study of disease by chemical methods, that is, the field of chemical pathology.

Systemic Effects of Infection

In all infectious diseases except the most trivial there are systemic changes even when cultures show that no bacteria have left the local site. It must be assumed that these lesions are related to toxic substances formed in the local focus, either by the bacteria or by

especially the peripheral sinusoids, are seen to be dilated and filled with large mononuclear cells, and occasionally with polymorphonuclear leukocytes and plasma cells. The cords of lymphoid tissue between the sinusoids are edematous, and the follicles are moderately prominent. The primary follicles are composed of numerous smaller secondary follicles with two or three large pale cells in the center of each. Bacteriologic culture of these nodes usually shows only a few bacteria, and it is generally assumed that this is a reaction to toxic substances and not directly to the contained bacteria. On the other hand, in lymph nodes draining purulent inflammation, many bacteria may be carried to the node and may produce small abscesses.

Lymph nodes draining a chronic infection

are only slightly enlarged and are firm. The microscopic changes are essentially the same, although there may be an increase of reticular tissue and fibrous tissue at the expense of lymphoid tissue.

In some infections all of the lymph nodes of the body are involved, and the process is not limited to those draining a local inflammation. This is particularly true in poliomyelitis, tularemia, and disseminated lupus.

Hyperplasia of Spleen. Similarly in many infectious diseases the spleen is enlarged, and

These cells not infrequently undergo necrosis and form irregular, hyaline, deeply acidophilic masses. In some infections such as typhoid fever the necrosis is conspicuous.

Hyperplasia of the Bone Marrow. In most infectious diseases the mobilization of polymorphonuclear leukocytes at the site of the inflammation is associated with hyperplasia of the bone marrow. The marrow is gray and cellular and contains numerous immature cells of the myeloid series. The discharge of these cells into the blood is responsible for the *leu-*

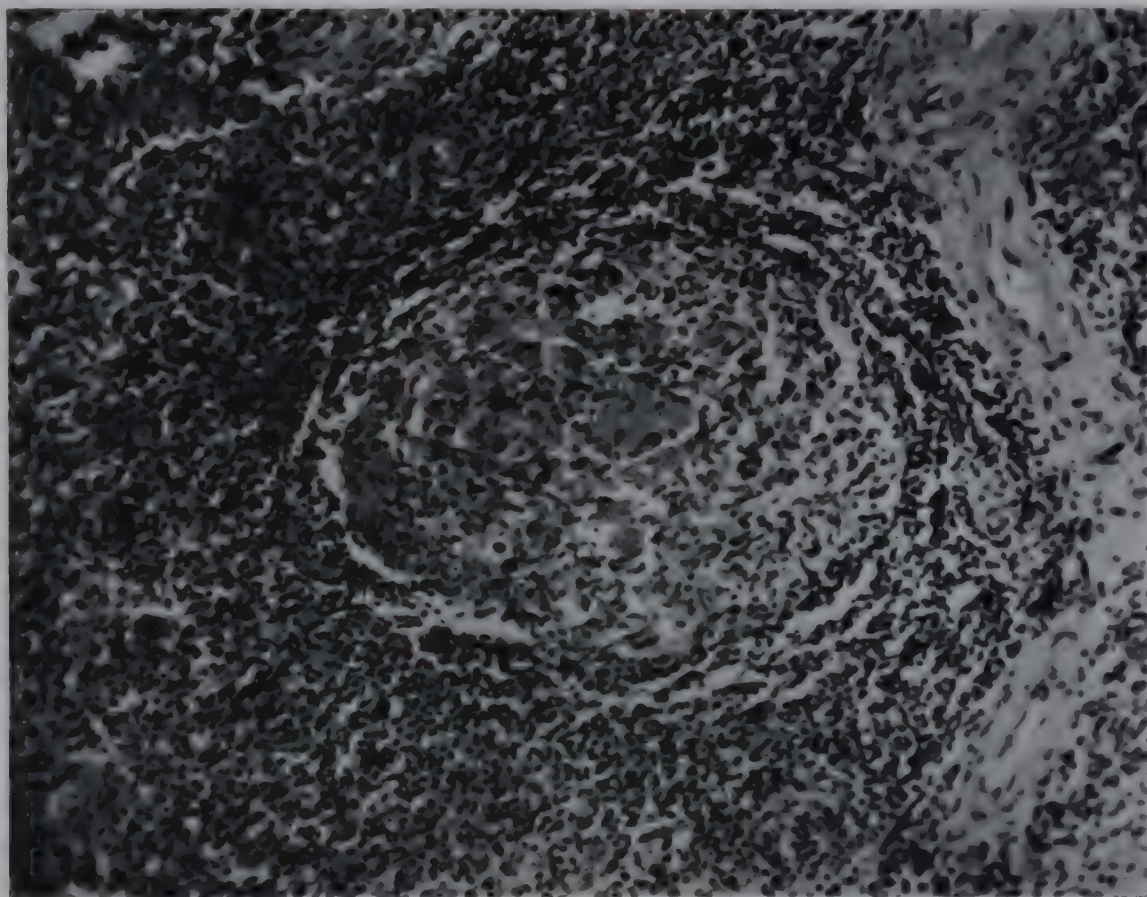


Fig. 91. Hyperplasia and necrosis of follicles of spleen.

the condition is known as “acute splenic tumor” or “hyperplasia of the spleen.” The spleen varies from 200 to 700 gm. or more in weight. The capsule is tense but not thickened, and when the parenchyma is cut it bulges from beneath the capsule. The pulp is red or gray and projects above the inconspicuous trabeculae and malpighian bodies. In most chronic infections the spleen is moderately enlarged and firm, and on section the malpighian bodies are distinct and enlarged.

The microscopic appearance varies. In some cases the malpighian bodies are unchanged, and the cords of the red pulp are infiltrated with an increased number of splenocytes, plasma cells, polymorphonuclear leukocytes, and eosinophils. In others the malpighian bodies are enlarged, and in the center of each there is hyperplasia of large pale cells.

kocytosis and for the appearance of immature cells—less segmented forms, myelocytes, and rarely myeloblasts—colloquially known as a “shift to the left.” In embryos the leukocytes mobilized in inflammation are for the most part formed locally (Canat and Opie).

Changes in the Viscera. In the solid viscera there are slight to moderate degenerative changes: cloudy swelling and fatty degeneration. In the skeletal muscle some of the fibers are swollen and homogeneous—Zenker’s hyaline necrosis. If this change is extensive, the muscle may rupture and a painful hematoma may form. The heart is frequently dilated and the muscle flabby. Most of the organs, especially the brain, are slightly edematous and hyperemic.

Changes in Endocrine Glands. There are consistent and prominent changes in the endo-

crine glands, important because of their possible role in explanation of physiologic disturbances. The *adrenal glands* are hyperemic and hemorrhagic. The yellow lipid early is uniformly distributed throughout the cortex, and after some days is completely lost, so that the adrenal cortex is a thin, dark-brown rim about a grayish white, firm medulla. In the cortex there are frequently foci of necrosis. Chemical examination of the adrenal medulla shows a decrease in the storage of epinephrine (from about 4 mg. per gland to 1.5 mg.) (Cramer).

tion of heat and increased production. Associated with fever, and possibly causing it, is a *reduction in the blood volume*, caused by a shift in water to the tissues and extravascular space. This anhydremia, together with the relative increase of water loss in sweat, leads to a decreased urinary output—*oliguria*, *retention of chlorides* in the extravascular fluid, and *hypochloridemia*. With a return of the temperature to normal, as in a crisis of pneumonia, the retained water and chlorides are promptly excreted by the kidneys and skin—

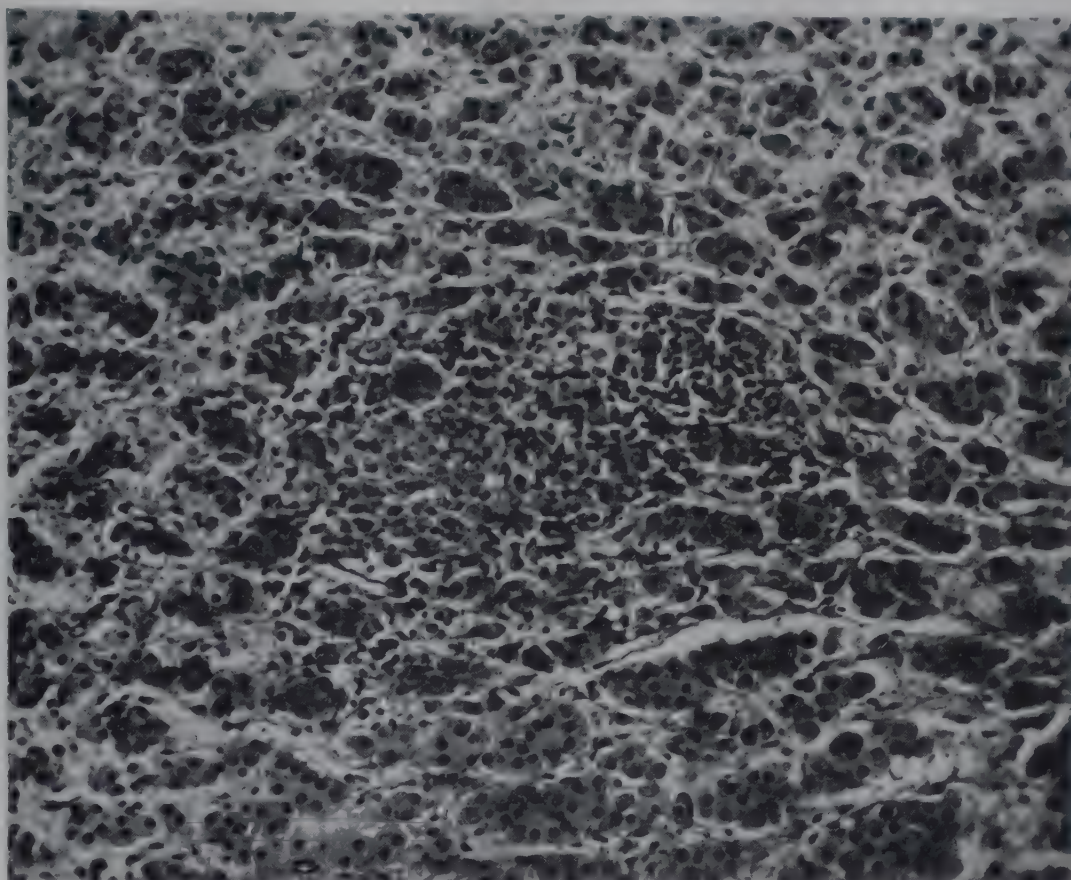


Fig. 92. Focal necrosis of adrenal in typhoid fever.

The *thyroid* is little changed in size but is hyperemic. The acini are smaller than normal, contain little colloid, and are lined by tall columnar cells (Goormastigh and Thomas). The *thymus* is reduced in size, with characteristic changes in the cellular types. There is no longer the sharp distinction between cortex and medulla, largely as the result of many lymphocytes within the medulla. At the edges of each of the lobules there is a moderate infiltration with eosinophilic leukocytes. This condition is frequently referred to as "accidental involution," to distinguish it from physiologic involution, which occurs at puberty.

Physiologic Lesions. The outstanding symptom of almost all infectious diseases is *fever*, probably resulting from action of the bacterial toxins on the heat-regulating centers of the brain. The basic defect is diminished elimina-

the *polyuria and excessive sweating* during the recovery stage of an infectious disease. In keeping with van't Hoff's law, the increased temperature induces an *increase of metabolism* (Du Bois). The discharge of stored thyroïdal secretion may also be responsible in part for the higher metabolism. An increase in metabolism means *greater catabolism of protein*, and hence there is an *elevated urinary excretion of nitrogen*, and correspondingly a demand for increased dietary intake of protein, the lack of which is related to the *loss of weight* in some infections such as typhoid. The increased metabolism in muscle exceeds the ability of the body to convert creatine to creatinine, and *creatinuria* may occur. The demands of the tissue with elevated metabolism cause in turn an *increase in pulse rate*, an *increased cardiac output*, and an *increase of*

respiratory rate—hyperpnea. The dilatation of wide areas of peripheral capillaries decreases the total effective resistance, and consequently the *blood pressure declines*, and the *pulse pressure becomes wider and often di-crotic* (Bazett).

A second outstanding symptom is *easy fatigability* as well as a *sense of tiredness*. Objective measurement shows a considerable *reduction in the efficiency of muscle*. The mechanism of this is not clear. The persistence of the fatigability into the convalescent period, when there is no fever, suggests that some direct injury to muscle by the toxins may be the agent (Simonson and Gollwitzer-Meier).

Disturbances in the motility and function of the gastro-intestinal tract—*anorexia and constipation*—are related to a similar inefficiency of the smooth muscle and possibly to damage to the hypothalamic centers related to appetite.

Headache is an almost constant symptom of many infectious diseases. The only tissues inside the cranial cavity which are sensitive to pain are the dura, the dural and larger pial arteries, and the dural sinuses. It follows that headache is related to tension or pressure on the vessels, possibly simple dilatation as in headaches produced by histamine (Clark, Hough, and Wolff). The edema of the brain occasionally found may also be important.

Disturbances in the metabolism of carbohydrates and to a less extent of proteins are a part of the more obvious toxemias (Holmes).

Systemic Invasion by Bacteria— Bacteremia, Septicemia, Pyemia

When bacteria are present in the blood as an incidental finding, the condition is known as “bacteremia,” while if they are present with their toxins in large numbers the term “septicemia” is usually applied. Most of the evidence indicates that the bacteria are not actually growing in the blood. Bacteria, especially staphylococci, may, after entering the blood, localize in numerous tissues and viscera and there form small abscesses—a condition known as “pyemia.” These abscesses are most frequently found in the kidneys, in the lungs, and in the heart muscle. Acute vegetative endocarditis frequently accompanies septicemia and pyemia.

Bacteriologic and Immunologic Studies in Infectious Diseases

It is frequently desirable or necessary to identify the causal agent of a disease. This should include isolation of the bacterium or other living agent in pure form and demonstration of it in the diseased tissue by special stains. The demonstration of specific immune bodies in the serum of a patient is of equal importance, and if possible two determinations should be made, one early in the disease and one late. An ascending titre of antibodies during the course of a disease is presumptive proof of the cause of a disease. If the anamnestic reaction and cross-neutralization can be eliminated, it is absolute proof (Cannon).

Chemotherapy in the Infectious Diseases

The concepts of Ehrlich in chemotherapy and his discovery of the effect of organic arsenic on the treponema of syphilis ushered in a new era in medicine. However, it was almost thirty years before the possibilities were fully realized with the studies on the sulfonamide compounds and the antibiotics such as penicillin, streptomycin, and others.

A chemotherapeutic agent may have two general effects. First, it may kill the bacterium or virus and thus suddenly terminate the progress of the disease. Or, second, it may inhibit further growth of the bacteria and leave final disposal of those already present to the defense mechanisms of the host.

Most of the chemotherapeutic agents, particularly the sulfonamides and the antibiotics, operate in the second way; that is, they are bacteriostatic. It is therefore of interest to the pathologist to examine the influence they have on the morphologic appearance of disease. This can be best done by specific examples.

Lobar Pneumonia. The typical course of lobar pneumonia results from the centrifugal spread of the inflammatory reaction throughout a lobe from the point at which the disease started. In any one part of the lung a series of changes follow the invasion by pneumococci. The initial reaction is an exudation of fluid and this is followed in three to six hours by emigration of leukocytes into the area. The pneumococci are promptly phagocytized and for all practical purposes the disease is under

control at this point. However, the centrifugal spread has continued. The bacterial invasion is always three to six hours ahead of the defense—the emigration of leukocytes—until the pleural surfaces are reached and further spread is impossible in this lobe (Wood and Irons).

Specific serum and chemotherapeutic agents prevent further growth of bacteria, which in turn stops centrifugal spread. Within three to six hours the leukocytes are in the advancing edge and the disease has been brought under control (Fig. 93).

zones. Leukocytes leave the capillaries and destroy the bacteria. The central core of necrotic tissue cannot be organized because there is no fibrin network for fibroblasts and capillaries to invade. Hence, it calcifies. In general, this process of organization of a vegetation takes four to six months (Moore).

Abscess. An abscess is a local destruction of tissue resulting from bacterial action. The central part is a semisolid or liquid mass of necrotic tissue and cells, and living and dead bacteria. The peripheral zone is living tissue containing the various cellular and humoral

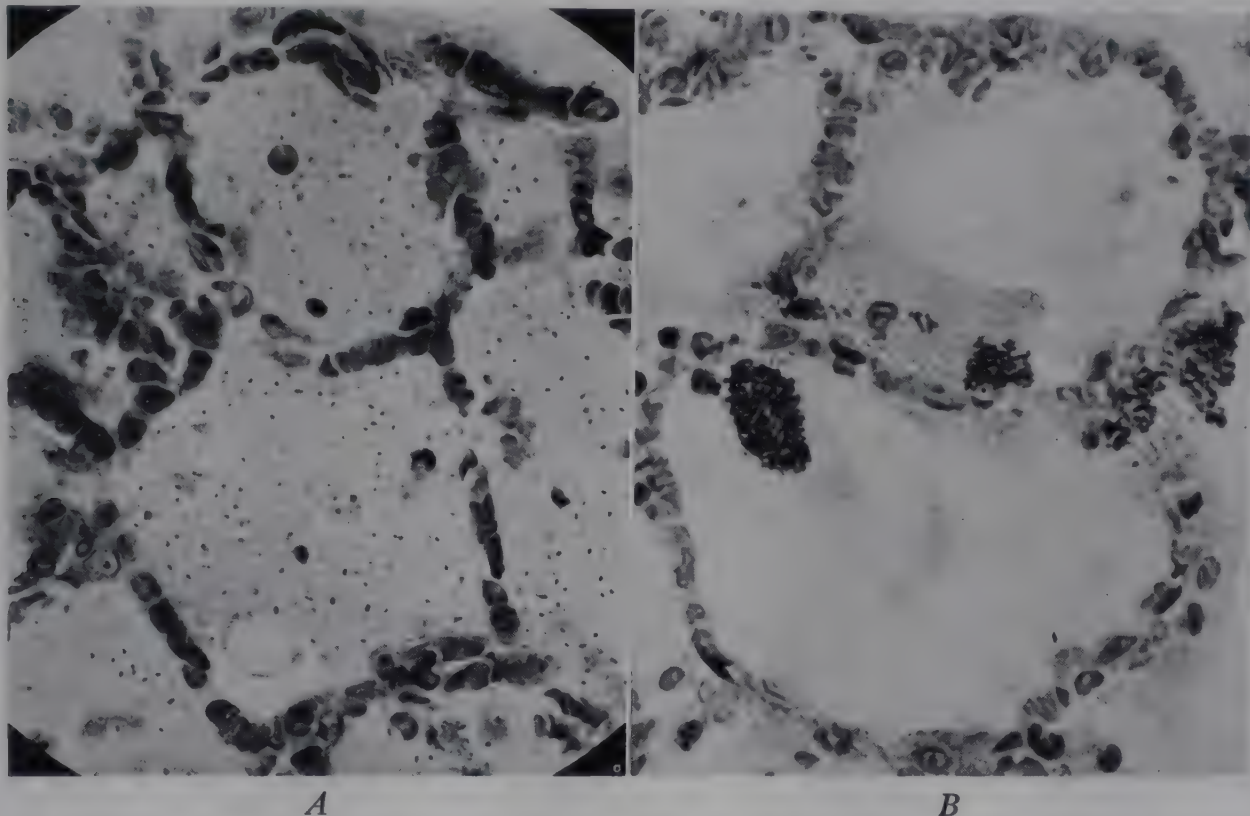


Fig. 93. *A*, Pneumococci in edema-filled alveoli in spreading lesion of a pneumonic process in a white rat twenty-four hours after intrabronchial inoculation. *B*, Comparable region in a rat six hours after treatment with specific serum given eighteen hours after intrabronchial inoculation. Note agglutination of cocci. (Photographs by courtesy of Dr. W. Barry Wood, Jr., identical with Figs. 3 and 11 of his article in *J. Exp. Med.*, Vol. 73.)

It should be emphasized that the serum or chemical does not bring the disease into control, but rather the normal defense mechanism accomplishes this end, with the aid of an agent that prevents further bacterial growth. Resolution then proceeds in the usual way.

Bacterial Endocarditis. The vegetation in bacterial endocarditis consists of three parts, a central core of necrotic valve, an intermediate zone of fibrin containing bacterial colonies, and a peripheral zone of fibrin. The administration of an antibiotic to a patient with bacterial endocarditis stops multiplication of the bacteria in the intermediate zone. Repair and healing can then proceed. Fibroblasts and capillary vessels grow into the two fibrin

elements of defense. If the balance between host and parasite favors the parasite the abscess will continue to grow in size by centrifugal destruction of the peripheral zone. If a bacteriostatic drug is given, further growth is stopped. All bacteria available to phagocytes are destroyed, but the bacteria in the center are not available. Most leukocytes which migrate into the necrotic center are destroyed.

If the abscess is of significant size, the center is liquid and cannot be organized in the absence of a fibrin network. As with pneumonia and endocarditis, the bacteriostatic drug does not cure the disease. Cure is accomplished by the normal defense mechanisms. In the case of the abscess, emptying of

the abscess by surgical incision will greatly accelerate healing. The necrotic debris is removed, the walls are brought into contact, and organization proceeds.

In all examples given it is clear that the effect on the bacteria by serum or chemical must be maintained until normal healing occurs. In pneumonia this is a matter of days or weeks, while in endocarditis it is months. Any decrease below the effective level during this period will permit the disease process to start to spread again.

Effect on Antibody Formation. When chemotherapeutic agents were first used, some expressed concern that the infection would be cured rapidly and there would therefore not be sufficient exposure to the bacterial antigens for antibodies to form. This has not proved to be true. In experimental pneumococcal infection in rabbits, control of the infection with penicillin twenty-four hours after subcutaneous inoculation had no influence on antibodies. With the sulfonamides, probably because they act more slowly, the drug may be started even earlier without influence on immunity (Harrison).

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XV

Streptococcal and Staphylococcal Infections of the Skin and Subcutaneous Tissues

The skin is the point of junction between the animal organism and the environment. Upon the integrity of the epidermis depends in large part the ability of the organism to prevent penetration of the deeper tissues by physical and chemical agents and by pathogenic micro-organisms. In addition to this protective function the skin has important physiologic functions: heat regulation through vasodilatation and evaporation of sweat, and possibly destruction of bacteria and of fungi by the static and lytic action of sweat (Bergeim and Cornbleet).

It is thus logical to begin the study of specific diseases with a consideration of those in which the portal of entry is the skin.

Normal Flora of the Skin. As the animal organism comes in contact with objects of the environment, micro-organisms are constantly deposited on the skin. The more common of these are the lowly pathogenic or saprophytic bacteria and fungi, but under special conditions pathogenic streptococci and staphylococci are encountered in cultures of normal skin (Downing, Nye, and Cousins).

Staphylococcal Infection of the Skin and Subcutaneous Tissues

Furuncles and Carbuncles. A furuncle or boil is an acute circumscribed inflammation of the skin usually resulting in local suppuration. A carbuncle is a complex furuncular lesion involving the subcutaneous tissue, from which the necrotic material is discharged through multiple openings.

Pathologic Anatomy. The initial lesion of a furuncle is an inflammation about a dermal gland or a hair follicle. In the adjacent dermal tissue there are infiltration with polymorphonuclear leukocytes, dilatation of vessels, and

exudation of fluid, so that a firm, spherical mass is formed. The central part undergoes necrosis and the whole becomes soft and fluctuant. The overlying skin is smooth and tense, and if the necrotizing process reaches the surface the skin is broken and the pus, frequently inspissated as a "core," is discharged. The cavity is filled with granulation tissue and the epidermis grows beneath the scab to restore the integrity of the part.

The carbuncle usually appears first as a focal induration in the subcutaneous tissue. There is progressive increase in size and spread laterally along the superficial fascia. The skin becomes elevated, tense, and dark red. At this stage there are edema, hyperemia, and infiltration with polymorphonuclear leukocytes. As the inflammation spreads laterally it ascends each of the perpendicular fibrous septa of the subcutaneous fat to reach the dermis. After some seven to fourteen days there are liquefaction of the inflammatory tissue at several points and discharge through multiple perpendicular tracts. Occasionally the entire region and overlying skin undergoes suppuration, leaving a large, ragged ulcer. Healing is by granulation and there is usually a scar. In both furuncles and carbuncles the regional lymph nodes may show acute hyperplasia, while in the latter there are frequently systemic symptoms of infection (Zeisler).

Predisposing Factors. The staphylococcus is the usual bacterial cause of furunculosis. Predisposing factors are concurrent diabetes, nephritis, avitaminosis, trauma, obstruction of the follicles from exposure to tar and paraffin, and excessive sweating. In most instances, the predisposing factors allow the staphylococci normally present on the skin to invade the dermis. Successive crops of boils are usu-

ally auto-inoculated. Occasionally in epidemics, the bacteria are passed from person to person directly or by fomites. The face, axilla, neck, buttocks, and leg are the most frequent sites.

Infections of the Face, Nose, and Lips. Three anatomic peculiarities of the face make infections of it especially dangerous: the muscles are not enclosed in fascial sheaths and

especially in epidemic form, begins with the formation of bullae over a limited part of the entire surface of the skin. These bullae are filled with a clear or an opaque fluid. The bullae rupture or dry up, and form scabs. In advanced cases there are numerous crops of the bullae and the entire body may be covered. The bulla forms at the junction of the rete with the stratum corneum. The dermis below

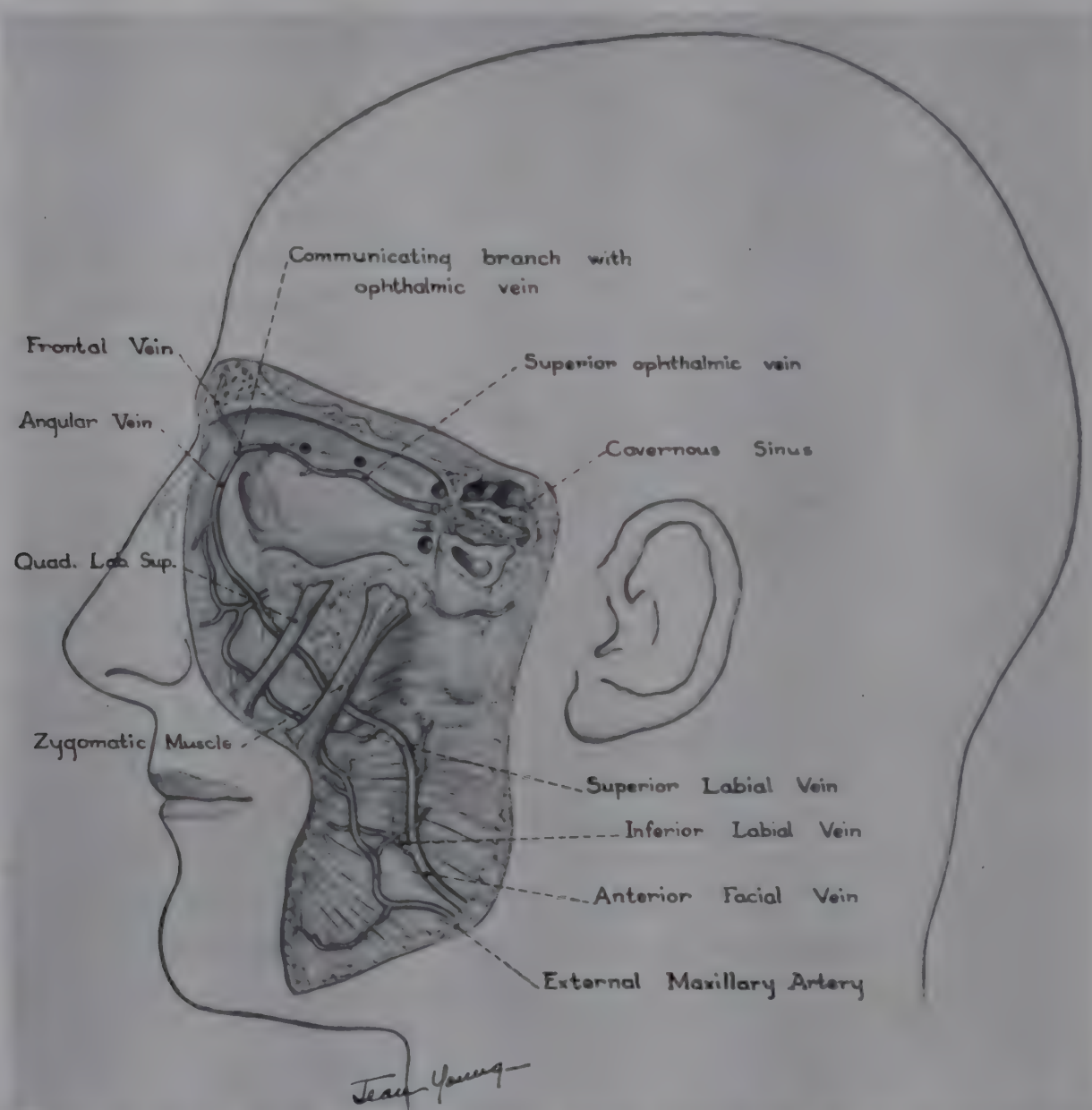


Fig. 94. Dissection showing course of the anterior facial vein and its anastomosis with the superior ophthalmic vein. (Adapted from Testut from Coller and Yglesias: Surg., Gynec. & Obst., Vol. 60.)

hence there are no fascial planes to limit the spread of infection; the muscles insert directly into the skin and are in almost constant motion, which tends to prevent localization; and the angular vein forms an anastomosis between the facial vein and the superior ophthalmic vein and cavernous sinus. Normally blood from the face flows through the facial vein to the internal jugular, but if these are occluded there is a reversal of flow and a thrombophlebitis of the cavernous sinus and a meningitis may follow (Coller and Yglesias) (Fig. 94).

Neonatal Pemphigus. Neonatal pemphigus,

is edematous and is infiltrated with lymphocytes and leukocytes; and the blood vessels are dilated. Changes in the viscera are inconspicuous unless a pyemia develops, in which case there are abscesses in the lungs, kidneys, liver, and spleen. From most cases *Staphylococcus aureus* may be cultivated, and similar organisms can be identified in sections of the bullae (Cole and Ruh).

Transmission. The causal agent of epidemic pemphigus is disseminated by attendants and by utensils used in the nursery. In many instances it has been necessary to close a maternity hospital and thoroughly disinfect all of

the rooms before an epidemic has been brought under control.

Neonatal Exfoliative Dermatitis. In separate epidemics, or coexisting with cases of neonatal pemphigus, there is another type of disease of the skin which differs only in the amount of desquamation, known as Ritter's disease (Schwartzman, Dragutsky, and Rook).

Acne. The role played by the staphylococcus in the causation of acne is questionable. The initial change is a plugging of the duct of a sebaceous gland and dilatation of the follicle. The epithelium of both the follicle and gland is invaded by polymorphonuclear leukocytes, and finally there is suppuration of the entire region. This progression of changes indicates that the primary cause of acne is a seborrhea, and that bacterial invasion is secondary. This assumption is supported by the high incidence at puberty (Hamilton).

Miscellaneous Staphylococcal Infections of the Skin. Included in this category are ecthyma (discrete epidermal abscesses in the superficial layers), infectious eczematoid dermatitis (spreading confluent inflammation with suppuration in the deeper layers of the epidermis), and pyogenic granuloma (a focal pedunculated mass of granulation tissue, projecting from the skin).

Staphylococcal Septicemia and Pyemia. Staphylococcal septicemia and staphylococcal pyemia occur half as frequently as similar lesions caused by streptococci. The primary site of infection is the skin in about one-third of cases, an osteomyelitis in another third, and some miscellaneous lesion in the final third. The mortality without specific treatment is between 80 and 90 per cent. The average duration of life is less than fourteen days. Anatomic lesions include acute vegetative endocarditis, multiple abscesses of the heart, lungs, kidneys, spleen, liver, adrenals, and brain, acute pericarditis and pleurisy, infected infarcts of the lungs, spleen, and kidneys, acute leptomenigitis, and cloudy swelling and fatty degeneration of the heart, liver, and kidneys (Neuhof and Aufses).

Streptococcal Infections of the Skin and Subcutaneous Tissues

The most important of the streptococcal infections of the skin and subcutaneous tissues are those of the hand and arm (Kanavel) and

the specific disease designated as erysipelas. Rarer similar infections of other parts of the body differ only as the anatomic structures involved vary. In most the cause is the introduction of virulent streptococci into a penetrating wound. Less commonly staphylococci and other bacteria produce the same lesions. The types of traumatism in order of frequency are: pin pricks, splinters, abrasions from contact with baskets, boxes, etc., lacerations from sharp instruments, bruises, and contusions. Most infections are caused by type A organisms (Keefer, Rantz, Shuman, and Rammekamp).

Felon. A felon is a suppurative inflammation of the peculiar, circumscribed, fibro-adipose tissue of the pad of the finger over the terminal phalanx. Pressure of the pus in this semiclosed space occludes the blood vessels and leads to necrosis of the bone. The infection later invades the bone and in children may cause separation of the diaphysis.

Paronychia. Paronychia begins as a suppurative inflammation of the tissue at one side of the nail, frequently from a hangnail. It spreads toward the base, and the entire eponychium is edematous and red, and pus can be expressed at many points. In a week or two the nail is lifted from the matrix by a collection of pus, and may be cast off. Granulation tissue grows from the matrix and projects from the base and sides of the nail.

Infections of the Minor Spaces of the Hand. In the hand there are several indefinite spaces that lie beneath the skin and along some of the fascia. Penetrating wounds that do not go deeply may enter these, and an infection becomes established. In manual laborers the epidermis and dermis are thick and fibrous, and an infection that begins in a subdermal space may rupture through the dermis at one narrow point and spread out laterally at the dermo-epidermal junction—a "collar-button abscess" or a "frog felon." Further extension may give rise to a series of lakes of pus, connected by narrow channels.

Tenosynovitis. In any infection of the hand, the inflammatory process may spread to the tendon sheaths by direct extension or by the lymphatics. Occasionally a wound may open the sheath and serve as the atrium of infection. The wall of the sheath is swollen and red, and the cavity is distended with a limpid or thick purulent exudate. The tendons are swollen

and soft, and in severe cases are fragmented and necrotic. Where the tendons pass beneath the anterior annular ligaments and the transverse carpal ligament both the sheath and the tendon may be necrotic and frayed. Necrosis of the sheaths at one or more points will allow rupture into one or more of the fascial spaces of the hand or forearm, into another sheath, or into a joint, with resulting suppurative arthritis, or erosion of bone and consequent

spaces. A purulent exudate accumulates, and the fibro-adipose tissue undergoes liquefaction. After spontaneous rupture or surgical drainage, the cavity fills with granulation tissue, and the resulting scar may involve the tendon sheaths, nerves, or blood vessels. The edema in the region where the median nerve passes beneath the anterior annular ligament may be sufficient to cause pressure necrosis of the nerve.



Fig. 95. Diagrams showing two types of arrangement of the flexor tendon sheaths. (Kanavel: *Infections of the Hand*. Lea and Febiger.)

osteomyelitis. In healing, scar tissue forms and results in adhesions within the sheath or contraction of the sheath or tendon with resulting limitation of motion (Flynn).

Infections of the Major Fascial Spaces. There are five major fascial spaces in the hand and one in the forearm: the middle palmar space, the thenar space, the hypothenar space, the dorsal subaponeurotic space, the dorsal subcutaneous space, and the major forearm space. Each is circumscribed by dense fibrous tissue, and infection may enter by extension from a tenosynovitis, by a penetrating wound, by the lymphatics, or by extension from other

Spread of the Infection. Cellulitis. Infection of the hand usually involves more than one structure. Infections involving the thumb, if spread is through the fascial space, come to the surface; if spread is through the tendon sheaths, they may rupture into the major forearm space or into the thenar space. Infections of the index finger may spread by the fascial spaces and point in the web between the index and the middle finger, or spread along the lumbrical muscle to the palm. If the tendon sheath is involved there is spread into the thenar space or rupture onto the surface. Infections of the middle finger along the tendon

heaths involve the middle palmar space and thenar space. Infections of the ring finger extend similarly into the middle palmar space or involve the lumbrical canal on either side. Infection in the fibro-adipose tissue may not become purulent, but may exist as a diffuse inflammation—cellulitis. The tissue is edematous, and when it is cut a quantity of limpid, cloudy, colorless or sanguineous fluid exudes. The cellular components are separated by an exudate composed of a protein-rich fluid, fibrin, polymorphonuclear leukocytes, and red blood cells.

lumen and inflammation of the adventitia and surrounding tissue—hyperemia, edema, and infiltration with polymorphonuclear leukocytes. Many bacteria are present in the thrombi and in the tissue. The lymph nodes are enlarged and soft. The substance bulges from the cut surface and it is finely granular and gray red. The sinusoids are distended with mononuclear cells and polymorphonuclear leukocytes.

Miscellaneous Infections. In patients with chronic lymphedema acute streptococcal cellulitis, rarely fatal, is common. Chronic ulcers



Fig. 96. Erysipelas of face.

Lymphangitis. In most severe streptococcal infections there is inflammation of the draining lymph vessels and nodes. The superficial lymphatics of the hand pursue the shortest course to the dorsum. The little finger and the ring finger drain directly into the epitrochlear nodes and then into the axillary nodes. A small percentage of infections beginning in the middle finger pass directly to the subclavian nodes above the clavicle. The lymph from the thumb and index finger drains into the axillary nodes. A small percentage of infections beginning in the middle finger pass directly to the subclavian nodes above the clavicle. The lymph from the thumb and index finger drains into the axillary nodes. In the inflamed lymphatic there is a thrombus in the

of the extremities in young adults are occasionally caused by streptococci (Taylor).

Erysipelas

Erysipelas is an acute cellulitis of the skin and subcutaneous tissues caused by the hemolytic streptococcus.

Pathologic Anatomy. In the region involved the skin is swollen and red, and there are vesicles or bullae in the epidermis or at the dermo-epidermal junction. The region is sharply outlined but short or long red streamers may extend into the surrounding tissue. In severe infections multiple small abscesses are present in the subcutaneous tissue, and necrosis of the skin may occur. The normal

elements are widely separated by a protein-rich fluid. The blood vessels are dilated and there is slight infiltration with mononuclear cells and a few leukocytes. Bacteria are readily demonstrable at the edge of the lesion but are absent or sparse in the center. The regional lymph nodes are large and firm, with the usual change of hyperplasia and occasionally supuration. In the viscera there may be the common lesions secondary to bacterial infection—cloudy swelling and fatty degeneration.

Clinical Types. In about 90 per cent of patients the face is involved, with a characteristic spread over the nose and cheeks: the butterfly distribution. Erysipelas of the newborn starts about the umbilicus or the genitals and the mortality is over 80 per cent (Culotta). Puerperal erysipelas beginning in the vulva may follow the usual limited course or may extend to the vagina and uterus as a characteristic puerperal infection. Erysipelas of the lower extremities is secondary to varicose ulcers or to chronic lymphedema. Surgical erysipelas is the type which spreads from an operative wound, notably from a mastoidectomy.

Causal Agent and Pathogenesis. With the exception of a very rare case, apparently caused by the staphylococcus, all erysipelas is caused by the hemolytic streptococcus. The bacteria enter the skin through an abrasion or wound, which may be healed by the time the erysipelas appears. In most patients there is a preceding upper respiratory infection, and manual transfer of the bacteria from the mouth to the skin is probable.

Clinicopathologic Correlation. The incubation period is two to three days and the usual course varies from four to ten days. Erysipelas is more common in the colder seasons, in children under two and adults over thirty-five, in debilitated persons, and in women at the time of menstruation. One attack does not confer immunity. The mortality, except in infants, is from 1 to 10 per cent, and varies directly with age and the presence of coexisting disease. In fatal cases, there is a bacteremia, and frequently a bronchopneumonia.

Human Bite—Morsus Humanus

The secondary infection in a human bite is usually mixed, but the spirochete and the fusiform bacillus are frequently found, and are largely responsible for the gangrenous char-

acter of the lesions. Other important bacteria are the staphylococcus and the streptococcus. The usual bite on the hand is inflicted by the teeth on the clenched fist. The extensor tendons within their sheaths and the capsules of the joints are under extreme tension, and the teeth penetrate into them. On relaxation the bacteria introduced are carried along the sheaths and into the joints. The break in the skin is closed. Anaerobic conditions for the growth of the organisms are thus established, and they multiply widely and rapidly through the tendon sheaths and fascial planes. There follows necrosis and gangrene. Human bites on other parts of the body are in general no different from other wounds (Boyce).

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XVI

Staphylococcal and Streptococcal Infections of the Bones and Joints

The logical sequence to the study of streptococcal and staphylococcal infections of the skin and subcutaneous tissues is a discussion of pyogenic inflammations of the bones and joints. In many instances, these are secondary to dermal infections, and most are caused by the staphylococcus and streptococcus.

Pyogenic Osteomyelitis

Osteomyelitis is a bacterial infection of bone and bone marrow. The bacteria may be brought to the bone by the blood (hematogenous osteomyelitis) or be introduced by way of a penetrating wound or a compound fracture (traumatic osteomyelitis). The disease may be of short duration (acute) or may persist for many months or years (chronic).

Acute Hematogenous Osteomyelitis. *Pathologic Anatomy.* The initial lesion of acute hematogenous osteomyelitis is a suppurative inflammation of the metaphyseal region. The bacteria localize in some instances in the subperiosteal tissue of the metaphysis and in others in the medullary cavity next to the epiphyseal cartilage. There are at least three reasons for the selective involvement of the juxta-epiphyseal region: the peculiar endarterial circulation of this tissue, possibly less active phagocytosis of the cells of the marrow at this point, and the frequency of trauma, and consequent disturbances of circulation and hemorrhage to form a focus of lowered resistance. The infection spreads in two directions, along the soft, newly formed, juxta-epiphyseal bone to the periosteum and juxta-articular tissues, and along the marrow to the diaphysis. When pus appears on the surface of the bone the periosteum is lifted and a subperiosteal abscess is formed. If it emerges on the intracapsular part of the bone, the periosteum may be perforated and a secondary suppurative ar-

thritis be established. If the exit is below the joint capsule, the periosteum is rarely perforated, but is stripped except at the points where the ligaments, fascias, and muscles attach. Thus the periosteal vessels are damaged and the circumferential circulation is impaired. Further extension into the diaphysis is by direct invasion through the marrow, or by re-penetration to the marrow from the periosteum by way of the haversian canals.

As in most suppurative inflammations, there is thrombosis of the adjacent vessels. This, together with the tearing of the periosteal vessels and the direct lysis of bone by the enzymes of the leukocytes, leads to the death of a part of the bone, known as a sequestrum. The surrounding living bone proliferates, becomes more dense, and highly calcified—the involucrum. Occasionally the infection spreads into the subcutaneous tissues over the bone (Beekman).

Thus in the typical advanced case of acute osteomyelitis the overlying skin and subcutaneous tissues are edematous and hyperemic. The periosteum is elevated, and next to the bone is a lake of pus. The cortical bone is eroded and small spicules of dead bone can be picked from the surface. The marrow cavity is converted into pus, and many of the trabeculae are loosened and float in the liquid.

Rarely, the initial focus of suppuration in the metaphysis or diaphysis is localized and does not spread. A wall of granulation tissue is formed about the central necrotic cavity, and the whole constitutes a Brodie's abscess.

Causal Agents and Incidence. Acute hematogenous osteomyelitis is characteristically a monostotic disease of the lower extremities, caused by the staphylococcus. There is a 7 to 3 preponderance in the male sex; almost all examples are in children under twelve, the bones of the lower extremities are involved three

times as often as those of the upper extremities; 85 per cent of cases are caused by *Staphylococcus aureus*. The portal of entry of the bacteria is sometimes difficult to demonstrate, but in about one-half of patients a furuncle or infected wound of the skin appears to be chronologically related. In approximately one-fourth there is a history of trauma to the bone a few days before the onset of the disease.

Clinicopathologic Correlation. As in all rapidly formed, space-consuming lesions in bone and in the periosteum, there is extreme pain from the expanding pressure. Systemic signs of an infection vary with severity and acuteness. Without treatment, the suppuration continues until it reaches the surface and discharges through a fistula. In some instances, there are recurrent attacks with relative quiescence between the exacerbations. There is a positive blood culture during the first few days in over half the cases. The mortality before the days of chemotherapy was about 25 per cent, but now should not exceed 7 per cent. In fatal cases there are persistent bacteremia and frequently metastatic abscesses in the viscera and a vegetative endocarditis.

Traumatic and Secondary Osteomyelitis. Included in this category are examples of osteomyelitis following penetrating wounds and compound fractures, and those resulting from direct extension from nearby infections. The pathologic changes are similar to those of hematogenous osteomyelitis, except that the lesion is not in the metaphysis but is contiguous to the preceding suppuration or trauma. In those related to compound comminuted fractures, sequestra are common, and pyogenic inflammation or gas gangrene of the soft tissues is a frequent complication.

Chronic Osteomyelitis. Either a hematogenous or a secondary osteomyelitis may persist for months or years, and take on the character of a chronic suppurative inflammation. Over the involved bone there are numerous fistulous tracts through the skin and the subcutaneous tissue is indurated and adherent to the bone. Throughout the bone there are many abscesses and sequestra, surrounded by involucra. The periosteum is thickened and many irregular osteophytes project from the surface.

Chronic Sclerosing Osteomyelitis (Garré). In some instances staphylococci are recovered from the tissues of chronic sclerosing osteomyelitis, but not in all. A long bone, most fre-

quently the tibia, is enlarged in a fusiform fashion over a distance of several centimeters. The cortex and medulla are fused, and the small amount of remaining bone marrow is replaced by fibrous tissue, infiltrated with lymphocytes and monocytes. There is no suppuration. Great care is necessary to differen-

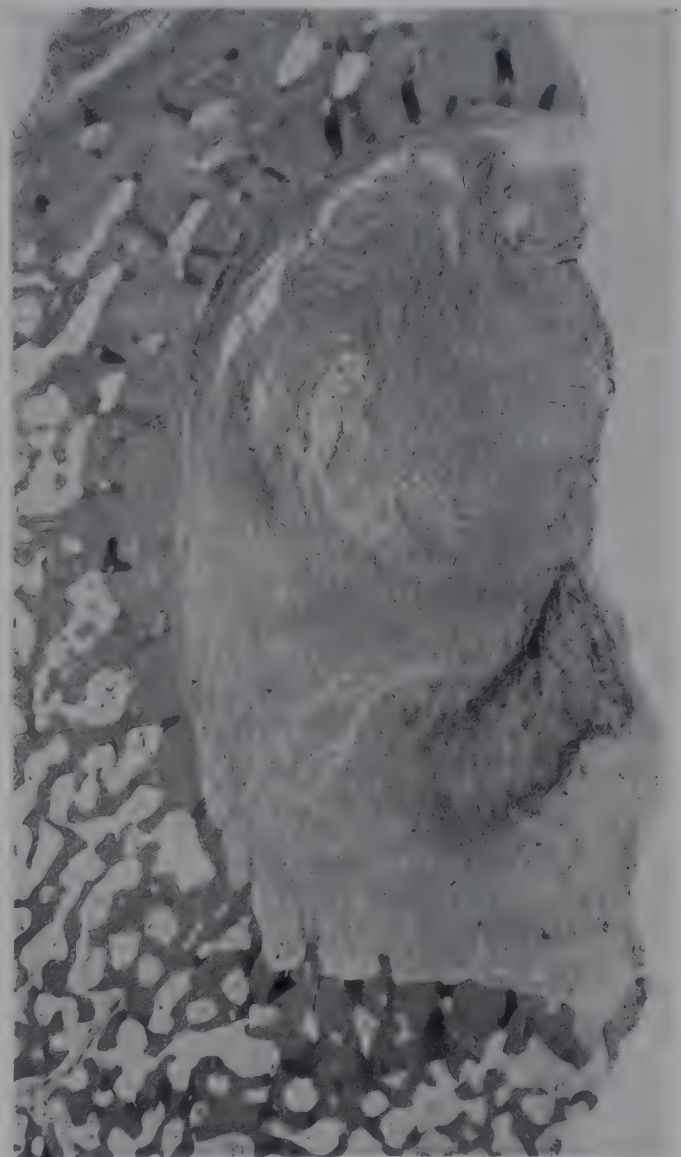


Fig. 97. Brodie's abscess of bone. (Armed Forces Institute of Pathology, Neg. No. 60638.)

tiate the lesion clinically from endothelial myeloma (Jensen).

Pyogenic Arthritis

In contrast with pyogenic osteomyelitis, pyogenic arthritis is a disease of all ages that is caused by any of a wide variety of bacteria.

Pathologic Anatomy. The pathologic changes are essentially those of suppuration within the joint cavity. The periarticular tissues and synovial membrane are edematous and hyperemic, and are infiltrated with leukocytes. The cavity is distended with pus. If not adequately and promptly treated the articular cartilage at the points of contact undergoes dissolution, and the underlying bone is ex-

posed. In the reparative process the bone proliferates, fills the defect, and covers part of the surrounding cartilage. The central destruction of cartilage in pyogenic arthritis serves to distinguish it from tuberculous arthritis, in which the erosion is peripheral (Phemister). Extension into the underlying bone from a hematogenous arthritis is unusual.

Pathogenesis. The bacteria reach the joint through penetrating wounds, by extension from the surrounding soft tissues and bone, or by the blood stream. Hematogenous arthritis is a recognized complication of puerperal infections, typhoid, meningococcal meningitis, gonorrhea, and pneumococcal pneumonia.

Clinicopathologic Correlation. The inflammation in the joint leads to swelling, redness, rigidity, and pain. The destruction of articular cartilage is reflected by permanent limitation

of motion or ankylosis—a fact to support the urgency of early treatment. The joints most frequently involved are, in order, the knee, hip, shoulder, wrist, and ankle (Reich).

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XVII

Infections Acquired from Contaminated Soil and Inanimate Objects

The clostridia are unique among the bacteria causing disease. Their main habitat is the soil and some are normal inhabitants of the intestinal canal of man and animals. They are introduced into abrasions and wounds by contamination with soil and feces, and may produce no disease, immediate overwhelming disease, or a latent infection which only becomes manifest after further trauma to the original wound. Under certain conditions they proliferate locally and elaborate a powerful exotoxin that is absorbed by the blood and lymph.

Kataphylaxis. Clostridia in the soil are almost exclusively in the form of spores, and the initial change of the bacteria in a contaminated wound is germination to the vegetative form. This step is not possible in living tissue, hence the spores may remain inactive in wounds for a long time and produce no symptoms. Tulloch found *Clostridium tetani* in 19 of 100 wounds of soldiers in World War I who were free of symptoms. On the other hand, if necrosis occurs as the result of trauma, from the presence of foreign bodies, or from the action of other bacteria or chemicals, germination proceeds and the disease is established. This phenomenon of the need of secondary or accessory factors in clostridial infections is known as "kataphylaxis," and is the basis of the immediate treatment of all contaminated wounds by removal of the dead tissue and foreign material—débridement.

Tetanus

Tetanus is an infectious disease caused by contamination of wounds with *Clostridium tetani* and characterized by hypertonus of the voluntary muscles, usually accompanied by spasms and convulsions.

Pathologic Anatomy. The anatomic lesions of tetanus are minimal and not characteristic.

The inflammation in the wound and in the nerves leading from the wound is probably caused by other bacteria. Swelling, chromatolysis, vacuolation, and nuclear displacement of the motor ganglion cells of the spinal cord may be an agonal or postmortem change. The edema, hyperemia, and petechiae of the brain and cord possibly result from the violence of the convulsions (Baker).

Pathogenesis. *Clostridium tetani* remains at the site of entry and does not invade the body. A powerful exotoxin is elaborated by the vegetative forms of the bacilli. How this toxin reaches the central nervous system to irritate the anterior horn cells and cause the hypertonus has not been definitely established. The preponderance of experimental evidence indicates that it enters the nerve at the motor nerve endings and travels along the axis cylinder. Tetanus does not follow peripheral inoculation if the motor nerve endings are not intact or if the nerve is cut; and the incubation period varies directly with the distance of the site of inoculation from the cord (Abel, Hampil, Jonas, and Chalian).

Causal Agents. Bacteriologic proof of the existence of tetanus is difficult and often impossible to secure. Examination of smears of the exudate from a suspected wound may show typical bacilli with round terminal spores. The material from the wound may be cultured anaerobically. Two animals should be injected, one with the suspected material alone and the other with suspected material plus 500 units of antitoxin. Toxin in the spinal fluid may be identified by similar control inoculations of mice or guinea pigs. Since the pathologic changes are nonspecific it is of the utmost importance that the pathologist use bacteriologic and immunologic methods to establish the diagnosis of tetanus.

Incidence. Certain wounds are more likely

to be contaminated with the spores of tetanus bacilli than are others: war wounds, the stump of the umbilical cord, wounds from blank cartridges and fireworks, surgical wounds, when there is contamination of the catgut, and the wounds incident to smallpox vaccination. Most of these special types have been eliminated by the proper use of antitoxin, prophylactic immunization with toxoid, improvement of the techniques of surgery and obstetrics,

armed forces. Fixation of one of the toxins—tetanospasmin—by the motor nerve cells and hyperirritability of the reflex nerve centers is responsible for most of the signs and symptoms. Depending on the location and extent of the involvement, three clinical forms are recognized: local, general, and cephalic. Death usually results from asphyxia incident to spasm of the muscles of respiration or of the larynx. Less common causes are broncho-

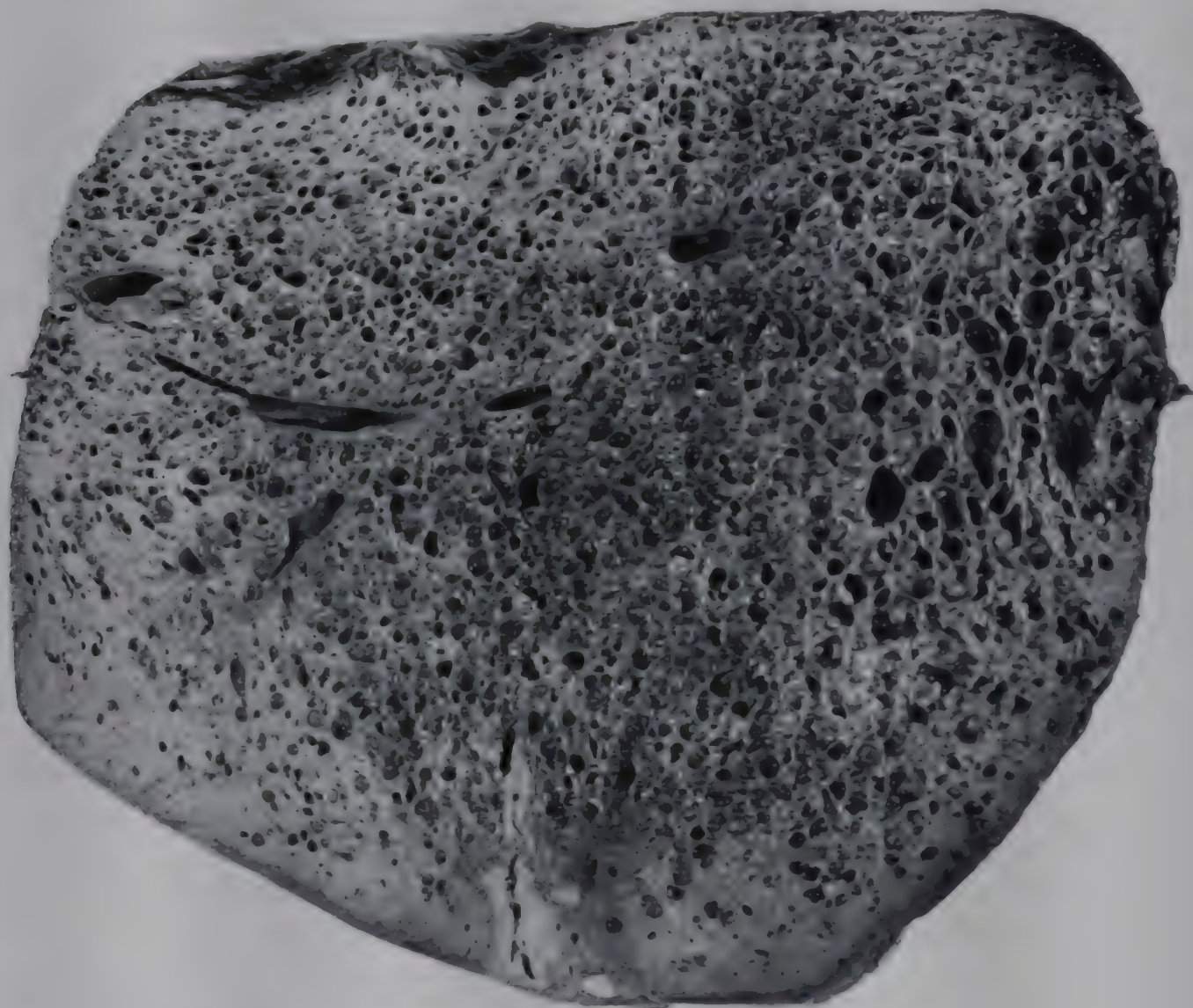


Fig. 98. Liver in generalized gas-bacillus infection.

and laws forbidding the sale of fireworks. This leaves only the sporadic civilian case of tetanus following contamination of wounds. Tetanus is more common in the tropics and in small villages.

Clinicopathologic Correlation. The incubation period varies from two days to a year. The mortality of untreated cases varies with the incubation period: 90 per cent if under six days and 50 per cent if over ten days. Therapeutic use of antitoxin has reduced the mortality to about 40 per cent, and the prophylactic use of toxoid and antitoxin has reduced the mortality to a negligible figure in the

pneumonia, exhaustion, and hyperpyrexia (Vinnard).

Gas Gangrene

With the advent of modern surgery gas gangrene almost disappeared as an entity, except for a few examples after severe compound fractures and during the puerperium following criminal abortion. However, in the early days of World War I, it again became an important disease—in 1914, 12 per cent of the wounded in the British Expeditionary Forces had gas gangrene, with a mortality rate of 25 per cent.

Most of our modern knowledge came as a result of the investigations of the British (Medical Research Committee) and the French (Weinberg and Séguin) bacteriologists assigned to the problem during and after World War I. Further studies were made in World War II (Langley and Winkelstein).

Pathologic Anatomy. In virulent infections there is, within eighteen to twenty-four hours after injury, edema in the region of the wound. The skin is tense and pale, and a dirty brown, limpid, foul-smelling fluid exudes from the break in the skin. Within the next twenty-four hours, there is further swelling, the skin becomes dark reddish purple and hard, and vesicles form in the epidermis. The tissues are separated by a thin serosanguineous fluid and bubbles of gas, and the muscle and other tissues are converted into a gelatinous, red, friable, translucent mass. The adjacent vessels are filled with thrombi. At the edge the necrosis advances along the bodies of the muscles and does not ordinarily spread across fascial planes. There is little or no cellular reaction, and only a few mononuclear cells and polymorphonuclear leukocytes are seen in microscopic sections. In the tissues, especially those adjacent to the bubbles of gas, are large numbers of bacilli. The degree of gas formation, autolysis of tissue, and exudation of fluid varies with the predominant organism: conspicuous gas production with the saccharolytic clostridia, typified by *Clostridium welchii*; prompt and widespread autolysis with the proteolytic clostridia, exemplified by *Clostridium histolyticum*; and excessive edema with *Clostridium oedematiens*.

In the terminal stages bacteria invade the blood and are distributed throughout all the tissues. Under certain conditions small amounts of gas may form in the viscera during life, but the characteristic crepitation in the organs of systemic gas bacillus infection at autopsy is a postmortem phenomenon. The liver, spleen, kidneys, and other organs and tissues are large and soft. The parenchyma is separated by innumerable bubbles of gas (Fig. 98). Bacilli are abundant in the walls of the bubbles, but there is no cellular reaction. The adjacent cells are partly or completely autolyzed.

Causal Agents. Bacteriologic study of cases of gas gangrene reveals a number of both

anaerobic and aerobic bacteria, the most important of which are: *Clostridium welchii*, *Clostridium oedematiens*, *Clostridium sporogenes*, *Clostridium fallax*, and *Clostridium septicum*. The more frequent aerobes are diplostreptococci and bacteria of the genus *Proteus*. Usually it is difficult to decide which of the numerous species present is the causal agent. It is probable that some of the aerobic and anaerobic bacteria serve as kataphylactic agents.

Isolation and identification of the numerous organisms should be done by cultural methods and inoculation of animals. Advantage may be taken of differences in optimal cultural conditions, varying degrees of pathogenicity, and inhibition in animals of some bacteria with specific antisera.

Clinicopathologic Correlation. Aside from the local manifestations, there are systemic symptoms caused by the exotoxins. Activity of the hemolysin and leukocytolysin results in the severe anemia and leukopenia respectively. The rare leukocytosis may be attributed to secondary infection with pyogenic cocci. Antitoxic and antibacterial sera are useful in prophylaxis and treatment.

Clostridial Infection in Animals. The more notable of these infections are blackleg in cattle, sheep, and swine (*Clostridium chauvei*), braxy in young sheep (*Clostridium septicum*), black disease of sheep (invasion of the necrotic foci in the liver caused by the fluke *Fasciola hepatica* with *Clostridium oedematiens*), and dysentery of lambs (*Clostridium welchii*, type B).

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XVIII

Infections Directly and Indirectly Transmitted from Animal Reservoirs

There are many diseases and latent infections which occur normally in animals and which are acquired accidentally by man.

Animal Reservoirs. Some of the more serious conditions contracted by man from animal reservoirs are: rabies from dogs; rat-bite fever, trench fever, infectious jaundice, plague, and endemic typhus from rats; glanders from horses; anthrax from cattle; trichinosis from hogs; tuberculosis in part from cattle; tularemia from rabbits; ringworm from cats; brucellosis from cattle and goats; and fleas, ticks, and hookworms from dogs. It is notable that this list includes diseases caused by viruses, rickettsiae, bacteria, spirochetes, fungi, protozoa, and metazoa, and that most are acquired from domestic animals and rodents that frequent human habitations.

Modes of Infection. The methods of transfer of pathologic micro-organisms from animals to man are of three general types: (1) direct or contact infection, (2) indirect, through water, soil, food, or air, and (3) by an intermediate host.

In this chapter the bacterial and spirochetal diseases transmitted directly and indirectly, with the portal of entry the skin, will be considered.

Tularemia

Tularemia has undoubtedly been present in the United States for many years, but was first recognized as a disease entity in man in September, 1912, when William B. Wherry of the University of Cincinnati isolated *Pasteurella tularensis* from a peculiar type of ophthalmitis in a butcher. The bacterium had been first recovered from rats and ground squirrels during the years 1908 to 1911 by Dr. George W. McCoy of the United States Public Health Service.

Pathologic Anatomy. The pathologic changes of tularemia are most conspicuous at the site of entry into the body, in the lymph nodes, and in the liver and spleen. At the point of entry on the skin an ulcer forms. The base of the ulcer is composed of necrotic tissue. The predominant cell is the mononuclear cell. The lymph nodes are greatly enlarged, especially the regional nodes draining the primary lesion, and on section small and large foci of coagulation or liquefactive necrosis are discernible. The foci of necrosis are surrounded by epithelioid cells and occasional giant cells. In the liver and spleen there are small, soft, yellow foci, 1 to 2 mm. in diameter, representing focal necrosis with histologic features similar to those in the lymph nodes. In 75 per cent of fatal cases there is tularemic pneumonia, characterized by lobar consolidation, focal or widespread necrosis of alveolar walls, and an exudate composed of fluid, fibrin, and mononuclear cells (Stuart and Pullen). Meningitis is observed (David and Owens).

Causal Agent. *Pasteurella tularensis* does not grow on ordinary culture media and requires blood glucose agar with added cystine (Ransmeier and Schaub). Morphologically it is a gram-negative, nonmotile, nonsporebearing coccobacillus. Guinea pigs die on the fourth or fifth day after inoculation. The lesions in animals are identical with those in man. The chorio-allantoic membrane of the embryo is a satisfactory medium for culture (Buddingh and Womack). There are apparently few viable bacteria in human tissues. Agglutinins appear in the blood of man at the end of the second week, and by the third week attain titres above 1 to 2500. A titre of 1 to 100 to 1 to 200 may be retained for many years if not for life. One attack of the disease confers absolute lifetime immunity.

Transmission. In the United States at the

present time most cases of tularemia are acquired by contact through the skin or eye with diseased rabbits. In certain parts of the west it is transmitted by the deer-fly, *Chrysops discalis*, by the tick, *Dermacentor andersoni* (By-

some indications that the bacteria may also enter the human body through the respiratory tract (Anschuetz), or the alimentary tract (Allen and Smith). In addition to the rabbit, the ground squirrel, the water rat, the dog, and



Fig. 99. Focal necrosis in liver in tularemia.

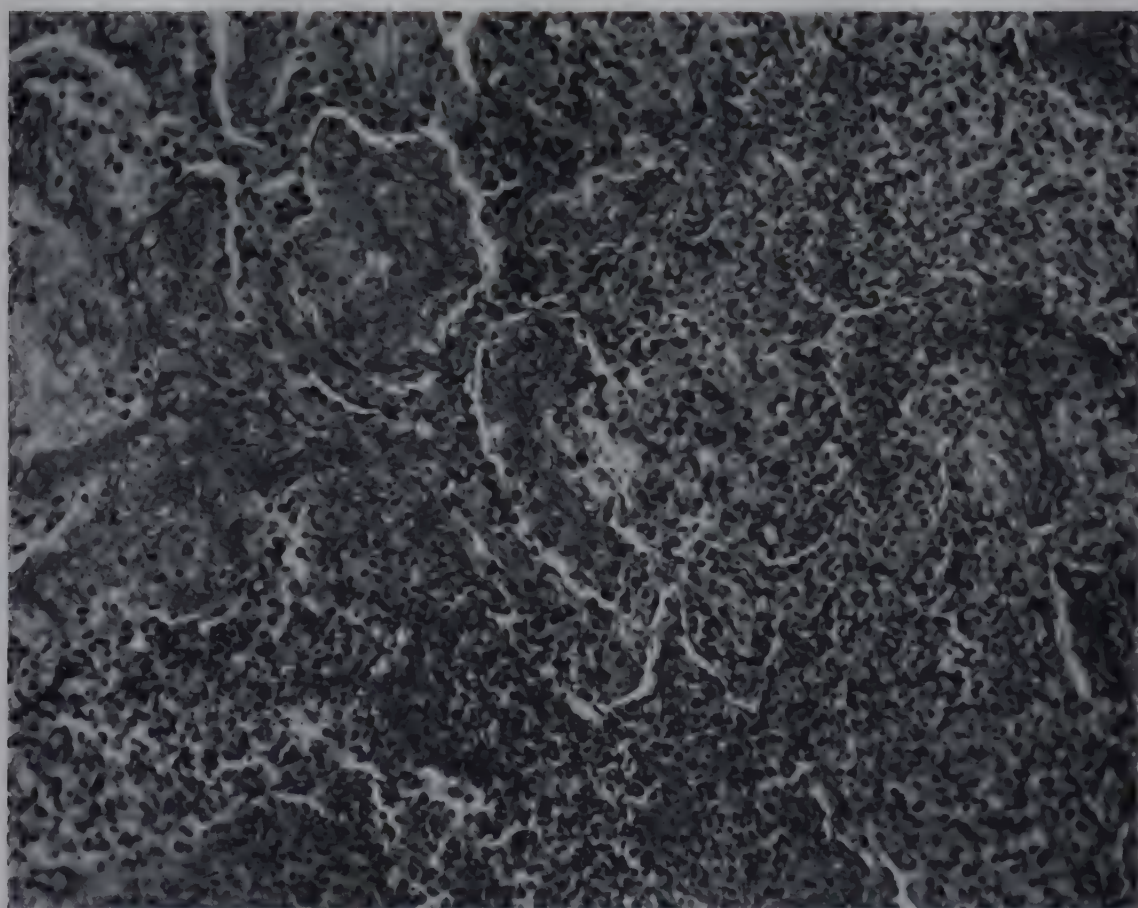


Fig. 100. Pneumonia in tularemia.

field, Breslow, Cross, and Hershey), and by the rabbit tick, *Haemaphysalis leporis-palustris*. The female tick transmits it to the eggs, larvae, and nymphs. Transmission from rabbit to rabbit is probably through the rabbit louse, *Haemodipsus ventricosus*. There are

possibly sheep, muskrat, opossum, woodchuck, and grouse may serve as animal reservoirs and possible sources of infection in man.

Accidental infection from laboratory animals is common, but transmission from man to man is rare. There have been no instances

of tularemia in pathologists except after a cut with the autopsy knife. Both of these phenomena are probably related to the scarcity of bacteria in human lesions as compared to those in the rabbit and guinea pig (Simpson).

Geographic Distribution. There are endemic foci of tularemia throughout the United States,

lesion is in the palpebral conjunctiva, and the preauricular nodes are enlarged; glandular, in which no primary lesion is demonstrable; and typhoidal, in which there is no primary lesion and no enlargement of the superficial lymph nodes. In all types there are the usual systemic signs of infection.

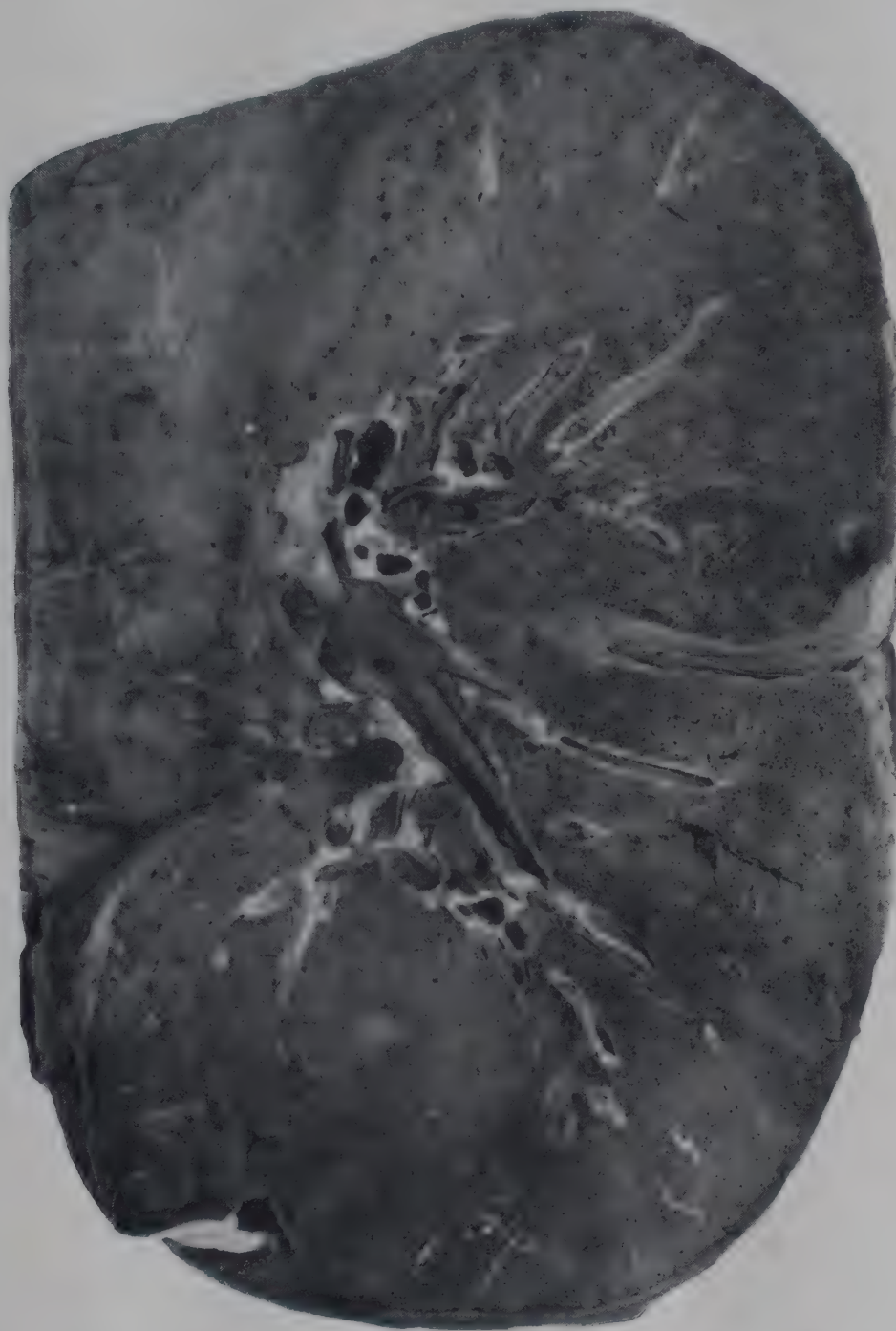


Fig. 101. The lung in glanders. (From a specimen in the Museum of Cornell University Medical School.)

but it is a rare disease in the New England States. It has also been reported from Japan and from Russian Siberia.

Clinicopathologic Correlation. The incubation period averages three days. The natural course is from two to three weeks. The mortality is about 4 per cent.

Types. Four clinical types are recognized: ulceroglandular, characterized by an ulcer of the skin and enlargement of the regional nodes; oculoglandular, in which the primary

Glanders

Glanders is a rare disease in man and is usually acquired by contamination of a scratch or wound with the nasal discharge or pus of a diseased horse, hence the high incidence in grooms and coachmen.

Pathologic Anatomy. At the site of entry into the skin an ulcer forms. From the ulcer indurated lymph vessels extend to the regional nodes. The nodes are large and soft and con-

tain numerous small abscesses. With systemic spread of the bacilli small abscesses appear in the skin, liver, lungs, spleen, and brain. In the lungs, the pneumonic consolidation and abscesses may become confluent. In all organs the histologic appearance and the pathogenesis of the lesions are the same. The initial reaction is an outpouring of serum, fibrin, polymorphonuclear leukocytes, and mononuclear cells. Within a few days there is lysis and the formation of an abscess. The mononuclear cells frequently contain characteristic large, lobulated, multiple nuclei. Infected thrombi in adjacent vessels are frequently present. In the lung there is a hematogenous, miliary bronchopneumonia that rapidly undergoes necrosis. Further growth in size is accomplished by centrifugal spread along fibrous septa and fascial planes. *Malleomyces mallei* is present intracellularly and extracellularly.

Causal Agent. *Malleomyces mallei* is present in the blood in the early stages of the disease and can be identified in stained smears and cultured from the pus of focal lesions. Glycerol agar or potato media should be used. It is pathogenic for most laboratory animals, and guinea pigs show a typical inflammation of the tunica vaginalis and die in fourteen days after inoculation—Strauss reaction. Many infections with glanders in laboratory workers have been reported. Complement binding bodies appear at the end of the second week of the disease. Agglutinins are present but inconstant.

Clinicopathologic Correlation. The incubation period varies from a few days to several weeks. Both acute and chronic forms are recognized. The mortality of the acute type approximates 100 per cent, and of the chronic is 50 per cent. The signs and symptoms, aside from those of an infection, are not typical. Relapses are common.

Melioidosis. This is a condition similar to glanders, found in Burma, the Malay states, and Indo-China, and caused by *Malleomyces pseudomallei*. In all organs except the brain there are small or large caseous nodules. The mortality is over 90 per cent. Death usually occurs within a week. Rodents, particularly rats, are the reservoir and man is infected by eating food contaminated with the urine of diseased rats. In the 1940's apparently indigenous cases were reported in the United States (McDowell and Varney).

Anthrax

Anthrax is an uncommon disease in man. The most frequent form is the malignant pustule acquired by contamination of abrasions or wounds with the products of infected animals. Less common are "woolsorters' disease," caused by inhalation of contaminated wool and hair, intestinal anthrax, following ingestion of contaminated food and drink; and a malignant pustule resulting from the bite of an insect that has just fed on an infected animal (Gold; Lucchesi and Gildersleeve).

Malignant Pustule. The first evidence of the disease is a small pustule on the face, neck, or upper extremities, rarely on the trunk or lower extremities. Within a day a vesicle forms on the surface and after rupture a serosanguinous exudate oozes from the surface. The fluid dries and constitutes a firm, adherent scab. The surrounding tissue is edematous and dark purplish red. Numerous secondary pustules and vesicles appear about the initial lesion. Throughout the entire region there are extreme hyperemia, edema, hemorrhage, and large numbers of polymorphonuclear leukocytes. In the center there is necrosis, and bacilli are present in large numbers. The regional nodes are large and edematous, and bacteria are easily demonstrated. The incubation period is less than three days. The natural course extends over one to three weeks. The mortality is about 20 per cent. Hyperimmune serum is useful in treatment (Ellingson, Kadull, Brookwalter, and Howe).

Pulmonary Anthrax. Woolsorters' Disease. The lesions are those of a bronchopneumonia and serofibrinous pleurisy. The tracheobronchial nodes are enlarged. The exudate consists of fibrin, polymorphonuclear leukocytes, and red blood cells, the latter accounting for the blood-streaked sputum.

Intestinal Anthrax. Ingested bacilli are destroyed by the gastric juice, but spores may survive and produce in the wall of the intestine either a focal lesion similar to the malignant pustule, or a diffuse phlegmonous enteritis. The inflammation of the intestine leads to severe abdominal pain, vomiting, and diarrhea.

Systemic Anthrax. In any of the forms of anthrax, but especially the pulmonary and intestinal, bacilli may invade the blood. Under these conditions there are enlargement of the

spleen and frequently a sanguinopurulent leptomeningitis. Recovery is rare in a true septicemia.

Causal Agent. In most fatal cases there is a septicemia, and *Bacillus anthracis* can be cultured from the blood as well as from focal lesions. Characteristic chains of large rods are seen in smears of the pus. Pathogenicity may be tested by subcutaneous inoculation of mice or guinea pigs, which die on the third or fourth day. There is a serosanguineous, gelatinous exudate in the tissues at the site of inoculation. Agglutinins and complement binding bodies are not demonstrable, but a saline extract of the infected tissues contains a precipitinogen that reacts with immune serum—Ascoli test.

Incidence. Hygienic conditions in factories dealing with animal wool and hides, and sterilization of shaving brushes, have materially decreased the incidence of human anthrax in the last two decades. Vaccination has lowered the incidence among animals. Herbivorous animals are most susceptible and the disease is found in all parts of the world. In animals the bacilli are transmitted through ingestion of contaminated food.

Erysipeloid

Pathologic Anatomy. In typical erysipeloid in man purplish red elevated lesions with a paler, less swollen central focus appear on the hand. There may be one or several discrete lesions, or they may be confluent. They are rarely present above the wrist, and lymphangitis and enlargement of the lymph nodes are rare. There is no suppuration. Microscopically intense hyperemia, edema, and hemorrhage into the dermis are observed. The basal cells of the epidermis are vacuolated. There is a moderate infiltration with lymphocytes and mast cells, especially in dilated lymphatics. Organisms can usually be demonstrated about the smaller capillaries, some of which are occluded by thrombi. Rare systemic complications are acute and chronic arthritis (Kartal-Zvolen), and an acute vegetative endocarditis (Russell and Lamb; Klauder, Kramer and Nicholas).

Causal Agent. *Erysipelothrix rhusiopathiae* is a small, slender rod, from 1 to 1.5 microns long. It is nonmotile and nonsporeforming, gram-positive, and nonacid-fast. It grows well

on plain or chocolate agar, or on Löffler's blood serum, both aerobically and anaerobically, and is cultivated with ease from a piece of excised tissue.

Transmission. The great majority of human infections are acquired from contact with swine or pork products, for example by workers in abattoirs. The next most common source is the handling and cleaning of fish. In some regions on the Atlantic seaboard of the United States the disease is initiated by the bite of a crab (Gilchrist). From these facts it is evident that it should be classed as an occupational disease. Accidental inoculation in veterinarians usually results in a severe form of the disease.

Clinicopathologic Correlation. The incubation period varies from one to three days. The inflammation of the skin spreads gradually in increasing circles, with some healing of the central portions. The mortality is low and recovery sets in after from five days to four weeks.

Rat-Bite Fever

The disease known as rat-bite fever may be divided into two types: one caused by *Spirillum minus*, and the other caused by *Streptothrix muris-ratti*. Both types are found in the United States (Brown and Nunemaker; Richter).

Rat-bite Fever Caused by Spirilla. After an incubation period of ten to twenty-seven days following the bite of a rat, there are chills, fever, headache, and malaise. The site of the bite, which is apparently healed, becomes swollen and red. There are a dark red macular or papular eruption over the body, pain in the muscles, and enlargement of the lymph nodes. Most patients recover, especially when treated with arsenicals. In the few reported autopsies degeneration of the tubular epithelium of the kidney and central necrosis and fatty degeneration of the liver have been noted. The other organs show only hyperemia and edema. *Spirilla* may be stained in the kidney. Similar lesions develop in guinea pigs, rats, and rabbits inoculated with tissue or blood, and the organism can be passed serially (Kaneko and Okuda).

Streptotrichal Rat-bite Fever. In this type there is a sudden onset of chills, fever, delirium, weakness, polyarthritis, and a maculo-

popular rash (Dawson and Hobby). In the autopsy report by Blake acute ulcerative endocarditis, subacute myocarditis, subacute hepatitis, subacute glomerulonephritis, infarcts of the spleen and kidney, and hyperemia and edema of the lungs were described. The organisms may be identified in the tissues and cultured from the blood or tissues. In culture the organism is associated with a small pleuropneumonialike organism, probably a variant rather than a contaminant (Dawson and Hobby). Agglutinins are present in the blood and are useful in establishing the diagnosis.

case, consist of jaundice, petechiae and ecchymoses throughout all of the tissues, and specific lesions in the kidneys, liver, and skeletal muscles. The kidneys are large and yellow, and bulge from beneath the capsule. The tubular epithelium shows cloudy swelling, necrosis, and deposition of bile pigment (Stiles, Goldstein, and McCann). The liver is normal or slightly enlarged, and is bile stained. Microscopically, proliferation of hepatic cells; cloudy swelling, fatty degeneration, and necrosis of hepatic cells; slight cellular infiltration; and biliary stasis are demonstrable. In

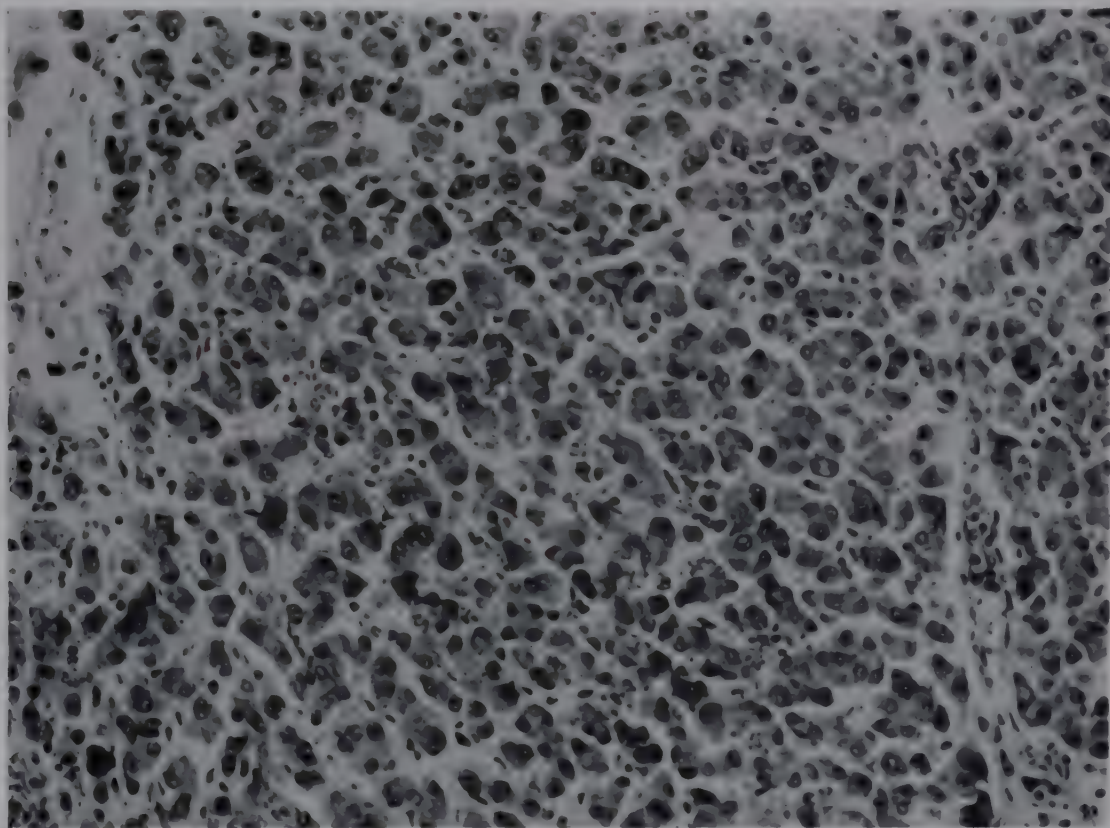


Fig. 102. The liver in infectious jaundice. (Photograph by courtesy of Prof. C. H. Hu.)

The organism is also known as *Actinomyces muris-ratti* and *Streptobacillus moniliformis*.

Haverhill Fever. This disease, originally named erythema arthriticum epidemicum, was first observed in Haverhill, Massachusetts, in January, 1926. The causative organism, originally named *Haverillia multiformis* (Parker and Hudson), is apparently identical with *Streptothrix muris-ratti* (Allbritten, Sheely, and Jeffers). The condition is characterized by a sudden onset, with a chill, a rubelliform or morbilliform eruption, and inflammation of the joints. The epidemic in Haverill was caused by infected milk from one dairy (Place and Sutton).

Infectious Jaundice

Pathologic Anatomy. The pathologic changes in infectious jaundice, or Weil's dis-

the skeletal muscles there are vacuolation, swelling, hyalinization, and cellular infiltration about single muscle fibers (Sheldon). The hemorrhages are a manifestation of damage to the endothelium of capillaries. In the spleen there are active erythrophagocytosis and hemosiderosis. Hemorrhage in the mucosa of the intestine may result in filling of the lumen with a tarry material (Ashe, Pratt-Thomas, and Kumpe).

Causal Agent. *Leptospira icterohaemorrhagiae* may be identified by darkfield examination of the blood plasma, and occasionally of the urine. After intraperitoneal inoculation of either blood or urine, guinea pigs develop a fever in from four to five days, and die in from seven to ten days. There are jaundice and petechiae throughout the viscera. *Leptospira* may be cultivated on special media. Immune bodies develop in man and in animals. A

therapeutic serum obtained by the immunization of horses or rabbits has proved satisfactory in treatment.

Transmission. Present knowledge indicates that man contracts the infection through the skin by contact with water contaminated with the feces and urine of wild rats, and that the disease may be controlled by the elimination of rats.

Clinicopathologic Correlation. The period of invasion of the body is marked by chills, fever, and prostration. After a period of four or five days, the pathologic changes in the liver are sufficiently advanced to result in jaundice, dependent on the inflammation and hemorrhage to the duodenal mucosa about the ampulla of Vater. The absence of bile in the intestine, together with the direct hepatic injury, probably produces a hypoprothrombinemia and the resultant hemorrhage so characteristic of the condition. The hemorrhages and inflammation in the gastro-intestinal tract may lead to mild epigastric pain and nausea. The degenerative changes in the kidney in the nature of bile nephrosis are responsible for the albuminuria and oliguria. Recovery usually begins about the third week (Molner, Meyer, and Raskin).

Varieties. In California and elsewhere there is a disease of dogs known as yellows or Stuttgart disease, caused by *Leptospira canicola*. Infection of man by this organism is called canicola fever. The course is mild and there is often no jaundice.

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XIX

Infections Transmitted by Insects

The importance of insects in the transmission of disease was first realized when Patrick Manson in 1878 observed the development of *Filaria bancrofti* in the mosquito. Since that time many diseases have been placed in this category: malaria, transmitted by the anophles mosquito, yellow fever by the aedes mosquito, epidemic typhus by the body louse, spotted fever by the tick, plague by fleas, relapsing fever by the louse and tick, and sleeping sickness by the tsetse fly.

Mode of Transmission. There are two general modes of transmission: biologic and mechanical. In biologic transmission the micro-organisms pass a part of the life cycle in the insects, as in malaria and yellow fever. If the asexual phase of the cycle is spent in the insect, it is designated as an intermediate host, while if the sexual cycle is in the insect it is the definitive host. In mechanical transmission the outer surface of the insect becomes contaminated with a micro-organism, which is then transferred directly to the susceptible host, as in the carriage of typhoid bacilli by the house fly. In the case of the tick transmitting the rickettsia of spotted fever, the micro-organisms are hereditarily transmitted in the insect host.

Plague

Plague has taken a tremendous toll of human life through the ages. The great plague of Justinian's reign and the Black Death of England in the fourteenth century are only two of over one hundred pandemics in the Christian era. The last sweep of plague around the world was at the close of the nineteenth century. The endemic focus for the world is India, where in the twenty years from 1898 to 1918 there were over ten million deaths from plague (White).

Types. It is customary to divide the clinical and pathologic manifestations of plague into three types: bubonic, pneumonic, and septicemic. The three types merge into one another, especially when the disease is fatal.

Pathologic Anatomy. In some persons the initial lesion of plague is a small vesicle of the epidermis formed at the point of the flea bite. This vesicle is filled with a slightly cloudy fluid, made so by polymorphonuclear leukocytes and large numbers of bacilli. There is usually no lymphangitis from this initial lesion to the regional lymph nodes. The pathologic changes in the regional nodes constitute the buboes of bubonic plague. The nodes are five to ten times normal size, the capsule of each is intact, and they are freely movable beneath the skin. The greater part of the medulla and at times of the cortex of the node is necrotic and is replaced by thick, yellow, semifluid material. There are advanced necrosis and infiltration with polymorphonuclear leukocytes (Fig. 104). There is a similar infiltration of the capsule and of the surrounding fibro-adipose tissue. In the lungs, especially in the pneumonic form, there is a bronchopneumonia, either discrete or confluent. The lungs are intensely hyperemic and on section a large quantity of red, frothy fluid drips from the surface. The areas of consolidation vary from 5 to 10 mm. in diameter, and are moderately firm and dark red or gray. Microscopically large numbers of polymorphonuclear leukocytes and red blood cells but little fibrin are seen. Necrosis of the alveolar walls and of the contained exudate is conspicuous. If the foci of pneumonia touch the pleural surface there is a localized acute fibrinous pleurisy. The liver is enlarged and throughout it there are small yellow foci of necrosis, composed of necrotic hepatic cells with large numbers of bacilli. The surrounding liver cells

are the seat of cloudy swelling and fatty degeneration. At times the spleen is enlarged and soft and contains foci of necrosis similar to those in the liver. Throughout the serous and mucous membranes there are numerous petechiae and ecchymoses varying from a dark red to black. The kidneys and the brain are

bodies in low titre, 1 to 40, are formed during the course of the disease. The organism is closely related to the various species of *Pasteurella* responsible for various septicemic diseases of animals, and to *Pasteurella pseudotuberculosis*, causing an epizootic disease of guinea pigs.

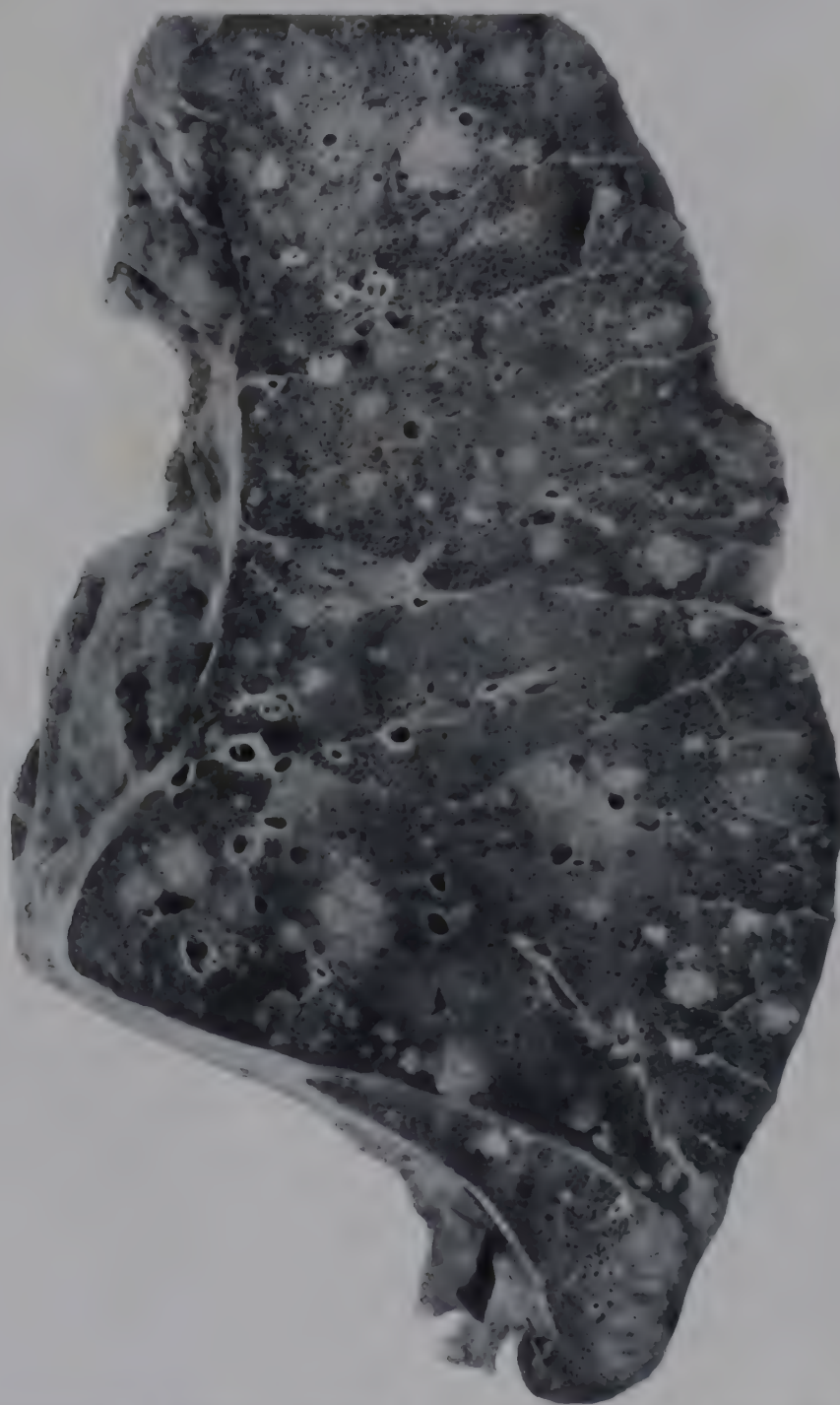


Fig. 103. Lung in pneumonic plague. (Armed Forces Institute of Pathology, Neg. No. 40656.)

hyperemic and edematous. The remaining viscera show no consistent pathologic change (Vint).

Causal Agent. *Pasteurella pestis* is a small, gram-negative, pleomorphic bacterium that grows slowly on artificial culture media. It is present in huge numbers in all of the lesions of plague and can frequently be cultured from the blood. It is pathogenic for rats, mice, and guinea pigs, and brings about death in these animals in from three to six days after subcutaneous inoculation. Agglutinating anti-

Transmission. The natural reservoir of plague is the rat. The disease is transmitted from rat to rat, from rat to man, and from man to man by fleas, chiefly *Xenopsylla cheopis* and *Ceratophyllus fasciatus*. Blood from an infected man or rat is sucked into the stomach of the flea and there the organisms undergo multiplication, so that the proventriculus may become completely blocked by a mat of bacteria. On the death of the host the flea seeks a new living host. During the process of sucking on the new host some of

the bacteria in the stomach are regurgitated into the wound. If the infective flea does not find a new host within a period of five to twenty days, depending upon temperature and humidity, it becomes free of pathogenic bacteria.

With the spread of plague to parts of the world other than the Orient, other rodents have become the reservoir. In South Africa it is the gerbille, in southwestern Russia the spermophile, and in Mongolia and Manchuria the tarbagan. Ground squirrels of the west-

fatal cases the predominating signs and symptoms are those of an overwhelming septicemia and toxemia. The organism elaborates a powerful exotoxin, and this induces locally necrosis and systemically weakness, fever, and coma. The mortality in untreated bubonic plague varies from 60 to 90 per cent, and in the pneumonic variety it is 100 per cent. Organisms are present in the sputum when there is a pneumonia, and it is possible that under conditions of intimate association the disease may be spread as a droplet infection.

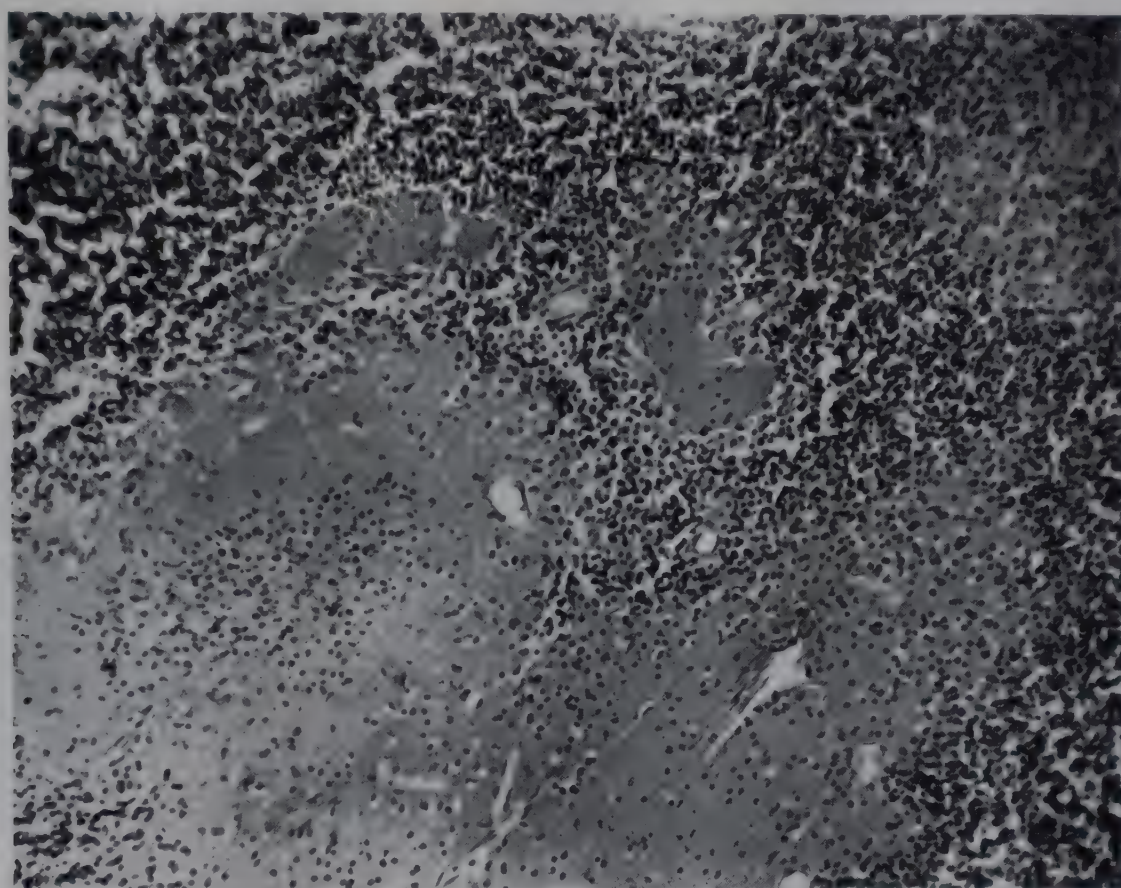


Fig. 104. Necrosis and edema of lymph node in bubonic plague.

ern United States have become infected, as well as field mice, prairie dogs, chipmunks, marmots, and cottontail rabbits. Despite the vigorous program of the United States Public Health Service, the disease "occasionally takes a human life, and it remains like a smoldering fire, ready to burst into flame at any time where the smoke of infection appears and adequate protective measures have not been applied" (Hampton). Control in an endemic focus depends upon eradication, as far as possible, of the animal serving as a reservoir, and on improving hygienic conditions, so that rats do not infest human dwellings. In areas free of the disease, continued freedom depends on the exclusion of rodents brought on board ship from endemic foci.

Clinicopathologic Correlation. The incubation period varies from two to five days. In

Diseases Caused by *Pasteurella Pseudotuberculosis Rodentium*. This bacterium is a rare cause of disease in man, and is closely related both bacteriologically and pathologically to *Pasteurella pestis* of plague and to *Pasteurella tularensis* of tularemia. The pathologic lesions are similar to those of tularemia and are found in the liver, spleen, and lymph nodes. Under natural conditions the organism is the cause of an epidemic disease in guinea pigs and in rabbits. An occasional case in man apparently follows contact with cats. The organism can readily be identified and cultured, and is pathogenic for mice and guinea pigs (Moss and Battle).

Relapsing Fever

Pathologic Anatomy. In relapsing fever it is difficult to separate lesions produced by the

spirochete and those resulting from complications usually present in fatal cases. The only organ in which the changes are unquestionably caused by the spirochete is the spleen.

pulp large numbers of spirochetes may be demonstrated. With the onset of a remission the spirochetes disintegrate and are broken into many small argyrophilic particles, and



Fig. 105. Worldwide distribution of plague.

The spleen is moderately enlarged and is firm, and malpighian bodies are conspicuous. Microscopically hemorrhage into the junctional pulp and hyperplasia of the reticulum cells of the white pulp are observed. Within the white

the follicle undergoes fibrosis (Russell). In most fatal cases there is bronchopneumonia, but this would appear to be caused by bacteria rather than by the spirochete.

Causal Agent. *Borrelia recurrentis* is pres-

ent in the spleen, blood, spinal fluid, urine, and prostatic secretion. It is pathogenic for guinea pigs and squirrels (Chung).

Transmission. In most parts of the world, notably China, Russia, and the Egyptian Sudan (Kirk), the spirochete is transmitted from man to man by the body louse. In parts of South Africa and the United States the insect vector is apparently the tick (Davis).

Incidence. Geographical Distribution. Relapsing fever is endemic or epidemic in China, India, and Russia (Shrimpton). Sporadic cases are seen in most other countries of the

Yaws

Some investigators believe that yaws and syphilis are identical diseases with different clinical manifestations, and others that there is a distinct difference in the two agents, *Treponema pallidum* and *Treponema pertenue* (Hamlin; Turner).

Pathologic Anatomy. Primary Infection. The initial lesion of yaws, frequently referred to as the "mother yaw," is most common on the foot and leg, but may occur on any part of the body. The fully developed lesion is a moderately well circumscribed ulcer, 2 to 4



Fig. 106. The spleen in relapsing fever. (Photograph by courtesy of Prof. C. H. Hu.)

world. It is present throughout all seasons of the year, but is slightly more common during the late winter and early spring.

Clinicopathologic Correlation. The signs and symptoms are essentially those of an overwhelming infection: fever, headache, chills, anorexia, and general aching in the bones and muscles. The pathologic changes in the liver and spleen bring about enlargement so that these organs are palpable. Damage to the liver or increased destruction of red cells is responsible for the occasional case with jaundice. There is no satisfactory explanation of the hemorrhagic lesions. The mortality rarely exceeds 10 per cent even in severe epidemics. The typical course shows many remissions and exacerbations, the former lasting from four to ten days and the latter from five to nine days (Chung and Chang).

cm. in diameter, from which a thin, cloudy fluid exudes. Microscopic examination shows that a part of the epithelial surface is lost but in areas where it remains there is conspicuous acanthosis and great lengthening and fusion of the rete pegs, so that a network of epithelium is formed in the deeper tissues. In the dermis and in the subcutaneous tissue there is infiltration with lymphocytes and plasma cells, particularly about the blood vessels. The presence of many polymorphonuclear leukocytes indicates the presence of secondary infection with bacteria. The blood vessels are slightly thickened, but there is not as much proliferation of connective tissue as in the chancre. With healing of the mother yaw a large, depigmented scar, surrounded by a zone of hyperpigmentation, persists for life (Wilson and Mathis).

Secondary Stage. Secondary lesions of yaws are more common on the skin than on the mucous membranes. They appear grossly as macules or papules, and rarely as larger confluent areas. Microscopically hyperkeratinization, acanthosis, and nodular infiltration in the dermis of lymphocytes and plasma cells are observed.

Tertiary Stage. The late or tertiary lesions of yaws are similar to those of syphilis, but

lymphocytes, identical with the similar lesions described in syphilis (Weller).

Causal Agent. With the usual silver impregnation method, the spirochete, *Treponema pertenue*, is readily identified in the mother yaw, occasionally identified in the secondary lesions, and rarely identified in the late lesions. In the lesions of the skin the spirochete is found in both the dermis and the epidermis. Inoculation of infectious material intratesticu-

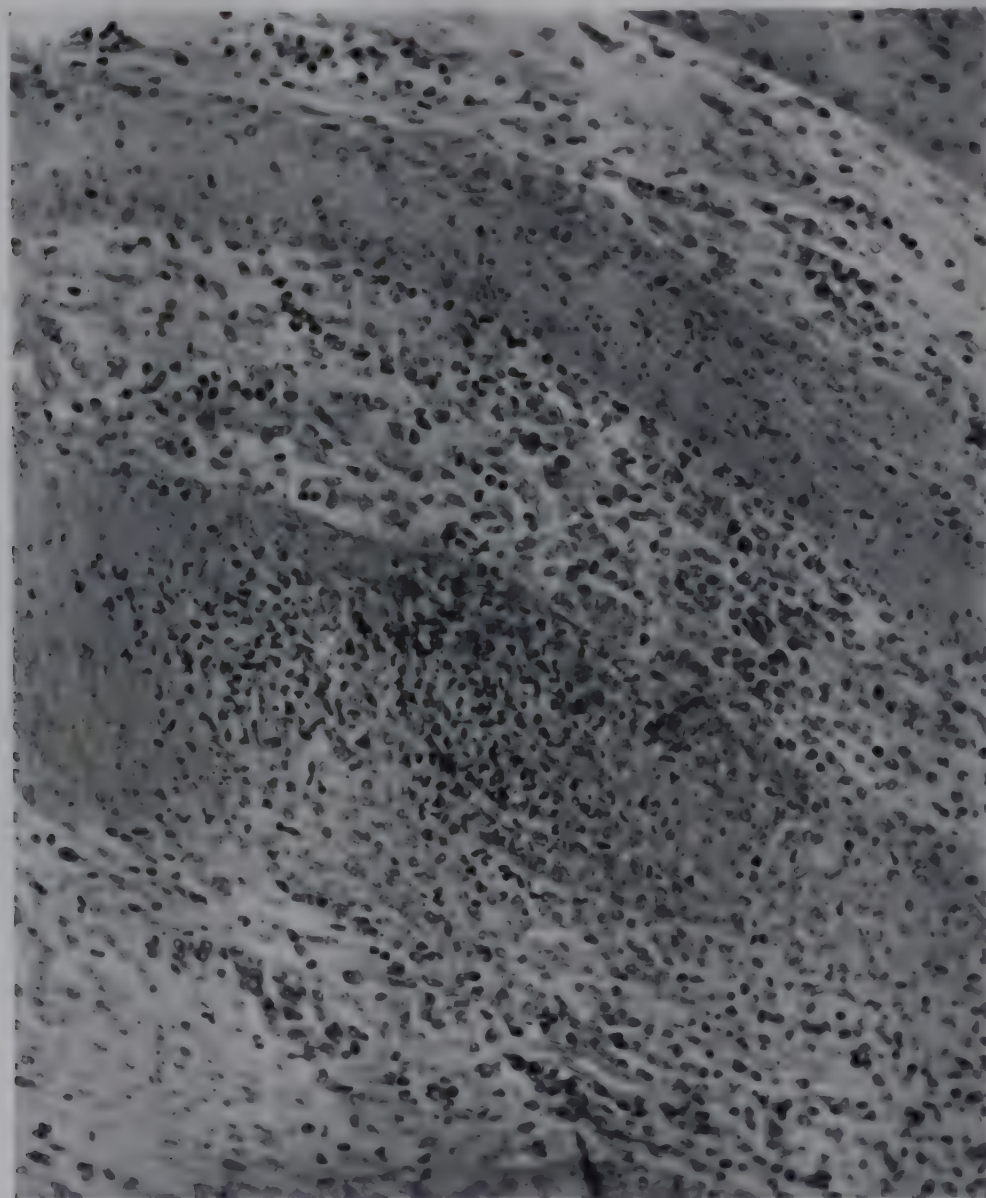


Fig. 107. Skin in yaws. (Armed Forces Institute of Pathology, Neg. No. 40227.)

differ in intensity and distribution. Areas of destruction of bone and areas of new formation of bone, particularly beneath the periosteum, are most common. Microscopically fibrosis, active formation of bone, and infiltration with lymphocytes and plasma cells are seen (Williams). Aneurysms of the aorta are uncommon, but histologic lesions of the aorta similar to, if not identical with, those of syphilis, are found in about one-half of all patients (Weller). Gross lesions in other organs are rare, but careful microscopic examination of the pancreas, testes, leptomeninges, and myocardium reveals fibrosis and infiltration with

larly into rabbits brings about definite changes in the testes (Turner and Chambers) different from those of syphilis (Turner and Chesney).

Immunity. A second attack of yaws is unusual, and experimental inoculation of infectious material into the skin of a person with active yaws produces no lesion or a lesion which heals in a short time. Evidence of a cross-immunity between syphilis and yaws is variable (Sellards). The Wassermann reaction is uniformly positive (Goodpasture and de Leon).

Transmission. Geographic Distribution. Yaws occurs in many parts of the world,

notably in moist, warm climates, in localities with a rural population, and in mountainous regions less than 2500 feet in elevation. Foci with a high percentage of infection are found in Australia, Melanesia, Polynesia, Malaya, and in certain parts of Africa, Central America, and South America. On the island of Jamaica, British West Indies, and in Haiti, about 70 per cent of the rural population have been infected by the age of twenty-five years (Hamlin; Saunders and Muench). The spirochetes are transmitted from an infected person with a superficial lesion to some minor traumatic wound on the foot of another person by flies. This transmission is purely mechanical (Lamborn; Kumm and Turner). Venereal transmission is unknown.

Congenital Yaws. The transmission of yaws from mother to offspring is extremely rare, if it ever occurs. This is in sharp contrast with syphilis.

Clinicopathologic Correlation. The most common symptoms of yaws is pain over the joints and bones, and this is probably referable to the periosteitis and osteitis. The lesions in the skin may be either nodules or ulcers. Nodules on the palms and soles with extreme hyperkeratosis over them are known as "crab yaws," and lead to considerable debilitation. An ulcer at the base of the nose involving the septum, the ala nasi, and the upper lip is known as "gangosa." Proliferation of bone on the nasal septum with the formation of an exostosis in yaws is probably responsible for some of the examples of goundou (Pardo-Castello).

Nonvenereal Syphilis. In various parts of the world there are diseases known by a local name similar to syphilis but not transmitted by sexual intercourse. An example of these is bejel of Syria (Hudson). Until more extensive and precise laboratory investigations are carried out it cannot be decided whether these represent yaws, nonvenereal syphilis, or some other spirochetal disease.

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XX

Infections in Which the Mode of Transmission Is Probably Human Contact

By contact infection is meant the spread of an infectious agent more or less directly from person to person. Although actual physical contact is not necessary, the association must be sufficiently intimate that infective material may be transferred. Of the bacterial diseases in which the bacteria enter through the skin, two are in this category: leprosy and pinta. In both instances the exact mechanism of transmission is poorly understood.

Leprosy

Leprosy is one of the oldest diseases known to man, and was the first against which public health measures were undertaken. Leprosy was also the first disease of man to be attributed to a bacterium; Hansen, after a visit with Koch in Berlin, described small bacillary bodies in the scrapings from leprous lesions of the skin.

Pathologic Anatomy. The significant pathologic changes in leprosy are in the skin and mucous membranes—the cutaneous type; and in the peripheral nerves—the neural type (Fite).

There are two distinctive lesions of the cutaneous type of leprosy: macules and lepromas. The macule is a circumscribed red elevation of the skin that gradually heals in the center and spreads peripherally. There is infiltration of lymphocytes and monocytes about the small blood vessels and epidermal appendages. This lesion is not distinctive, but the lepromatous lesion is characteristic. Small and large nodules are formed in the subcutaneous tissue, especially over the extremities and on the head. The tissue is grayish yellow and firm. Microscopically the typical leprous or foam cells are clearly seen. These large mononuclear phagocytes are arranged in small and large foci about the blood vessels, or

freely in the dermal and subcutaneous tissues (Tilden). Many leprous nodules undergo superficial ulceration and become secondarily infected with pyogenic bacteria.

In the neural type of leprosy the peripheral nerves show bulbous enlargement and are firm. There is proliferation of the fibrous tissue of the perineurium, and to limited extent of the endoneurium. Occasional small or large collections of leprous cells may be seen.

In advanced and fatal cases of leprosy there are small lepromas in the viscera, especially in the liver, spleen, and lymph nodes, just visible as yellow foci. They are composed of collections of leprous cells about the smaller blood vessels. The lymph nodes draining an involved area are irregularly enlarged and in advanced cases all of the lymph nodes are large and firm. These changes are caused by infiltration of leprous cells and by proliferation of fibrous tissue. The testes are atrophic and fibrotic.

Effect of Treatment. The histologic changes which follow treatment with promin are similar to those of spontaneous remission—gradual disappearance of acid-fast bacilli and atrophy (Fite and Gemar).

Causal Agent. In sections from leprous tissue, small acid-fast bacilli, 1.5 to 5 microns in length and 0.2 to 0.5 microns in width, are seen in the leprous cells. They have a tendency to be arranged in clumps or bundles, or occasionally appear as intracellular or extracellular fused masses, known as globi. In addition, many small granular coccoid, and polar types are seen in active lesions. Most attempts to grow *Mycobacterium leprae* on artificial media have failed, but Soule and McKinley have cultured an acid-fast organism on special media under an increased tension of oxygen and carbon dioxide. A precipitin reaction has been demonstrated. For some unknown

reason about 35 per cent of patients with leprosy have a positive Wassermann reaction in the absence of demonstrable syphilis.

not over 750 of these in the United States. Since many initial lesions are on the exposed parts of the body, it would seem that bacilli



Fig. 108. Leprosy involving the face. (Photograph by courtesy of Prof. C. H. Hu.)

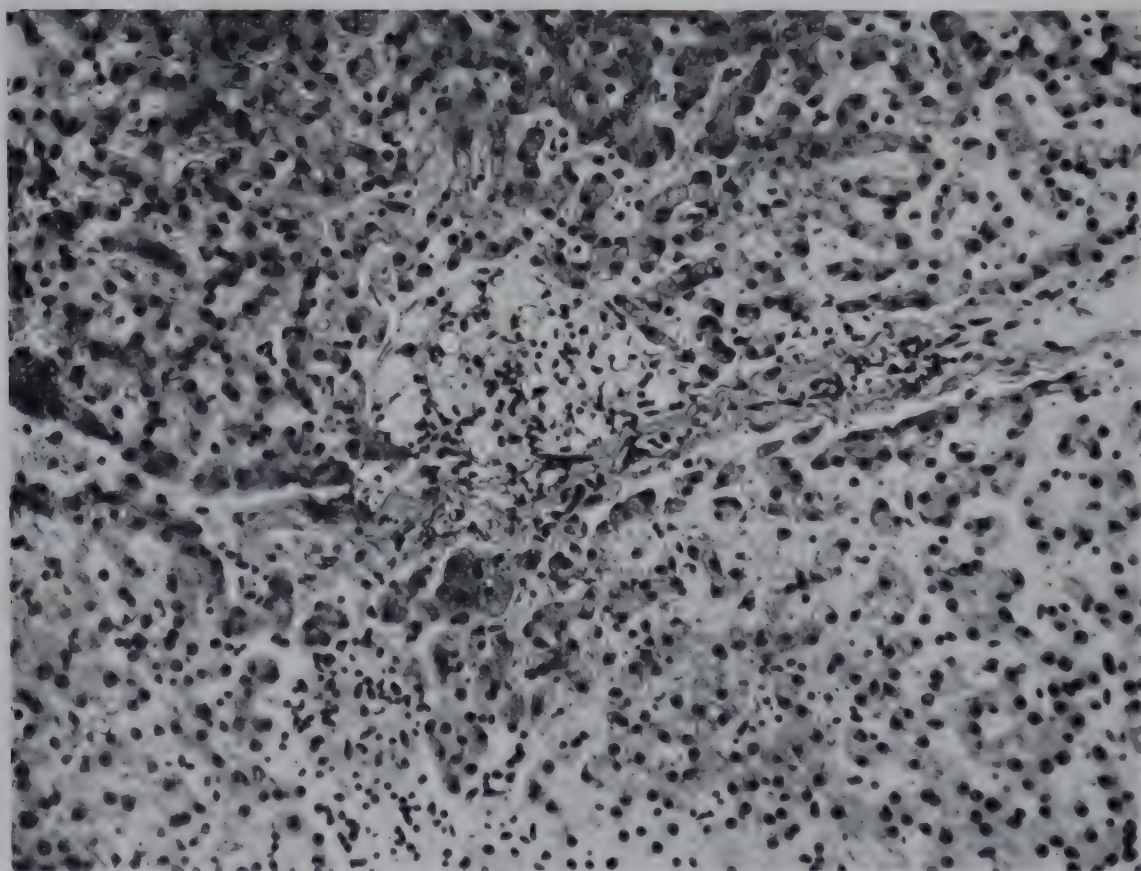


Fig. 109. Leprous nodule in the liver. (From a case in the files of the New York Hospital.)

Transmission. It is estimated that there are between two and five million people in the world today with leprosy, and that there are

enter the body through the broken skin. The occurrence of leprosy in families has been repeatedly noted, and from this observation

many investigators have postulated a hereditary susceptibility. This is further supported by the fact that this familial distribution seldom involves both members of a marital pair. A few American soldiers in World War II acquired the disease during service in regions of endemicity.

Clinicopathologic Correlation. It is difficult to determine the incubation period, but a conservative estimate places it at between five and ten years. Most leprosy is acquired in childhood, and men are three times as susceptible as women. The peak incidence of clinical leprosy is during the second decade of life. The involvement of the nerves produces anesthesia and muscular contractures. The anesthetized parts are more susceptible to trauma and infection, while the muscular contractures produce the characteristic deformities of leprosy. The leprous nodules in the skin of the face and mucous membrane are responsible for the appearance of the victims. The course of leprosy extends over many years, with remissions and relapses, but in most instances is steadily progressive. Death usually results from some complication, such as secondary infection or amyloidosis (Hopkins and Faget).

Pinta

Pathologic Anatomy. Pinta, like syphilis, is divisible into stages. The initial lesion is usually located on the extremities, more often on the lower extremity. The lesion is first a minute papule, surrounded by an area of hyperemia. It progressively increases in size and forms a large irregular patch of slightly indurated tissue, measuring from 10 to 13 cm. in diameter. Microscopically acanthosis and elongation of the rete pegs are seen. The epidermis is edematous and slightly infiltrated with lymphocytes. In the dermis there is an infiltration of plasma cells, lymphocytes, monocytes, and polymorphonuclear leukocytes, especially about the blood vessels. The endothelium of the capillaries is swollen. During the second stage, the stage of dissemination, numerous small macules and papules known as pintids appear over the entire body. These enlarge progressively and the initial lesion becomes indistinguishable from them. The microscopic picture is similar to that of the initial lesion. The late manifestations are most conspicuous in the skin. There are large, frequently symmetrical areas of depigmenta-

tion, surrounded by hyperpigmentation, on the extremities or on the trunk. There are no dopa-positive cells in the area of depigmentation, and there is slight fibrosis of the dermis and slight infiltration with lymphocytes. In these areas there are hyperkeratosis and atrophy of the epidermis. Lesions in the aorta and in the central nervous system have been described clinically but pathologic studies have not yet accurately defined them.

Causal Agent. The spirochete of pinta is morphologically identical with the spirochete of syphilis. It is easily demonstrated in the lymph in all lesions except the late atrophic depigmented areas. About 60 per cent of persons with pinta during the secondary stage have a positive Wassermann reaction, while almost all of those in the tertiary stage react. Experimental inoculation of persons suffering from pinta with the spirochete of syphilis has been successful, thus establishing it as a distinct disease. Inoculation of the skin of rabbits produces a papulovesicle (Leon Blanco and Oteiza).

Transmission. Pinta is more common in Negroes and Indians than in the white man. It occurs in Mexico, northern South America, and in Cuba. It is apparently transmitted by contact or by an insect vector. Venereal transmission has not been observed.

Clinicopathologic Correlation. The incubation period is seven to ten days, and the course extends over many years. There are few systemic symptoms. After a single injection with bismuth or arsenic the spirochetes disappear from the lymph within twenty-four hours (Pardo-Castello and Ferrer; Beerman).

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XXI

Upper Respiratory Infections

There are two ideas concerning the mode of transfer of bacteria from the respiratory tract of one person to that of another: the contact theory and the air-borne theory. The contact theory postulates that small droplets of fluid containing bacteria are projected into the environment by coughing or sneezing and immediately reach the mucosa of the nose or throat of the second person. The air-borne theory assumes that bacteria are thrown into the environment and are capable of surviving for a period of hours or days.

In recent years laboratory studies, clinical studies, and therapeutic tests have given convincing evidence in support of the air-borne theory. Laboratory studies have dealt with the ability of bacteria to survive in the dust and air of rooms, and with the demonstration that serologically identical types are responsible for outbreaks of disease which cannot be explained except as air-borne. Clinical studies have been directed toward an investigation of cross-infections in hospitals. For instance, a high percentage of children admitted to a scarlet fever ward will, before discharge, acquire a different type of hemolytic streptococcus in their throats. Therapeutically, ultraviolet light or aerosols have been tested and found effective in the prevention of cross-infection. Studies in the armed services during World War II supported the importance of air-borne infection and emphasized the role of carriers in disseminating the streptococci (Robertson).

*Inflammations of the Nose—
Common Cold*

Pathologic Anatomy. In acute inflammations of the nose the mucosa is swollen, soft, red, and velvety. Within the cavity of the nose there is an excessive secretion of thin

mucus or a thick yellow fluid. The swelling of the mucous membrane, especially that over the inferior turbinate bone, results in obstruction of the nasal passages. Microscopically the epithelium is observed to be swollen, and frequently the cilia are absent. The subepithelial tissues are edematous, and are infiltrated with lymphocytes, plasma cells, red blood cells, and polymorphonuclear leukocytes. The blood vessels are dilated.

Chronic inflammations of the nose may be of two types, hypertrophic or atrophic. Occasionally there are combinations of the two. In hypertrophic rhinitis the mucous membrane is thicker than normal as the result of proliferation of fibroblasts in the subepithelial tissue. The epithelium may retain the usual cylindrical character, or there may be metaplasia to a stratified, squamous type of epithelium. The thickening of the mucous membrane is in most instances irregular, so that sessile or pedunculated polyps are formed, which are of inflammatory origin.

In atrophic rhinitis the mucous membrane is thin and is composed of a superficial layer of columnar or transitional epithelium, and a dense subepithelial layer of connective tissue. There is atrophy or complete disappearance of the glands, so that there is an inadequate secretion of mucus.

Causal Agent. The most convincing evidence at the present time indicates that the common cold is caused by a virus. This statement is based on the observations of Dochez, Shibley, and Mills, and of Long, Doull, Bourn, and McComb, who succeeded in transmitting the common cold to human volunteers and to chimpanzees, with filtrates of nasal washings, in about one-half of their experiments. Topping and Atlas propagated a filterable agent in chicken eggs which produced a typical cold in human volunteers.

Inflammations of the Accessory Nasal Sinuses

Inflammations of the accessory nasal sinuses are similar to those in the nose. In acute inflammations there is swelling of the

trophic and an atrophic type of chronic inflammation of the sinuses. The polyps, common in the hypertrophic type, are sessile or pedunculated masses which project into the sinus or grow down into the nose and cause obstruction of the orifice of the sinus (Fig.



Fig. 110. Polyps of nose in association with chronic sinusitis. (Photograph by courtesy of Dr. Theo. Walsh.)



Fig. 111. Streptococcal pharyngitis in scarlet fever. (Photograph by courtesy of Dr. Malcolm Cook.)



Fig. 112. Scarlet fever. Note the distribution of the erythema, the circumoral pallor, and the blanching of the erythema by pressure of a hand on the abdomen. (Photograph by courtesy of Dr. Malcolm Cook.)



Fig. 113. Diphtheria. A dirty gray confluent membrane extends across the midline. (Photograph by courtesy of Dr. Malcolm Cook.)

mucosa, which may completely occlude the orifices of the sinuses. Secretion accumulates in the sinus, and in most instances is converted into a purulent exudate—empyema of the sinuses.

Pathologic Anatomy. There are a hyper-

110). The polyp is composed of a mass of loose mesenchymal tissue, infiltrated with lymphocytes, mononuclear cells, and plasma cells. There are occasional glands. The surface is covered by a stratified columnar epithelium, but there are occasional foci of

metaplasia to a squamous type. Infiltration of eosinophils in a polyp is considered by some to prove that the nasal inflammation is allergic. Within the mucosa of the sinus there is fibrosis of the subepithelial tissues, with atrophy of the glands and thickening of the blood vessels. The periosteum of the adjacent bone is thickened and there may be hyperplasia or osteoporosis of the underlying bone (McMahon).

Causal Agent. The causes of inflammations of the accessory nasal sinuses are essentially those of inflammations of the nose, although obstruction of the orifice of the sinus, with the accumulation of secretion, renders the secondary invaders—staphylococci, streptococci, and pneumococci—far more important.

Complications. Severe inflammations of the accessory nasal sinuses may ulcerate through the mucosa, and produce an osteomyelitis of the adjacent bone. In extension from the ethmoid and the sphenoid sinuses there may be thrombophlebitis of the cavernous sinus, or the formation of an extradural or subdural abscess or a brain abscess.

Tonsillitis. Pharyngitis. Laryngitis

Pathologic Anatomy. Pathologic changes in the common infections of the pharynx and larynx are similar or identical. The mucous membrane is swollen, velvety, and red. The surface is covered by a variable type of exudate: catarrhal, purulent, or fibrinous, depending on the bacterial cause and the severity. The lymphoid follicles in the submucosa are hyperplastic. The submucosa is edematous and is infiltrated with leukocytes, many of which are also present in the epithelium and in the exudate in the lumen. The blood vessels and lymphatics are dilated. Rarely there is ulceration.

In the tonsils the presence of crypts slightly modifies the picture. The crypts fill with exudate and are seen as small, gray or yellow flecks on the surface. Inspissation of this exudate and subsequent calcification produces the tonsillolith (Weller). On the other hand, the occasionally encountered small islands of cartilage and bone in the tonsil are probably rests of embryonic cartilage from the branchial arches (Moore).

In inflammation of any part of the respira-

tory tract the swelling of the mucosa and the filling of the lumen with exudate and mucus may obstruct the passage of air. This is more important at the normally narrow points: the nose, the larynx, and the smaller bronchi. Thus an acute laryngitis will produce more severe symptoms than a comparable pharyngitis, and the edema of the vocal cords may become so severe that a tracheotomy is required to relieve the obstruction.

In all upper respiratory infections there is a variable hyperplasia of the regional lymph nodes, and in severe infections there may be the usual systemic effects of a toxemia or bacteremia—hyperplasia of the spleen and cloudy swelling and fatty degeneration of the heart, liver, and kidneys. Local complications of the pharyngitis and tonsillitis include peritonsillar abscess and retropharyngeal abscess.

Peritonsillar Abscess (Quinsy). When the infection in the tonsils spreads to the surrounding tissue, the anterior pillars and the adjacent soft palate and uvula become red and swollen. The tonsil is pushed toward the midline and partially blocks the fauces.

Retropharyngeal and Lateral Pharyngeal Abscess. Following acute inflammations of the nose and throat or ear, some of the draining lymph nodes which are located beneath the posterior or lateral pharyngeal wall may undergo suppuration. The suppurative process extends along the fascial planes, and may be located between the pharyngeal wall and the cervical fascia, between the cervical and alar fasciae, or between the alar and prevertebral fasciae. In retropharyngeal abscess a fluctuant mass appears just to the side of the midline. In lateral pharyngeal abscess there is bulging of the tonsil or of the tonsillar pillars. In the more severe cases the inflammatory process extends into the superior mediastinum. The streptococcus is usually the responsible organism, but other bacteria may be isolated, alone or in combination with the streptococcus.

Clinically, there are the usual signs and symptoms of an acute inflammatory process. The mass of the abscess causes obstruction of both the respiratory and the alimentary tracts, and there may be some disturbance of speech. The abscess may not appear until many days or several weeks following the acute pharyngitis (Grodinsky).

Scarlet Fever

Scarlet fever is characterized by a sore throat and a diffuse rash, and is caused by the streptococcus. On the basis of the modern concept of the role of the streptococcus and its erythrogenic toxin, it is convenient to discuss scarlet fever under three titles: the primary lesion in the throat, the dermal lesions caused by the erythrogenic toxin, and changes in the viscera.

Primary Lesion. The tonsils are red and swollen, and on the surface there are frequently irregular, discrete patches of a grayish

puration occurs the reaction is one of hyperplasia and increase of mononuclear cells (Brody and Smith).

Dermal Lesions. The rash of scarlet fever appears on the second or third day of the disease. It is usually first visible on the thorax and neck, and spreads to the entire body within two days as a diffuse erythema, scarlet in color, with many closely set points of deeper red. After death the rash fades, and unless petechiae are also present no changes in the skin are visible at the time of the autopsy. Microscopic examination shows slight to moderate edema and hyperemia of

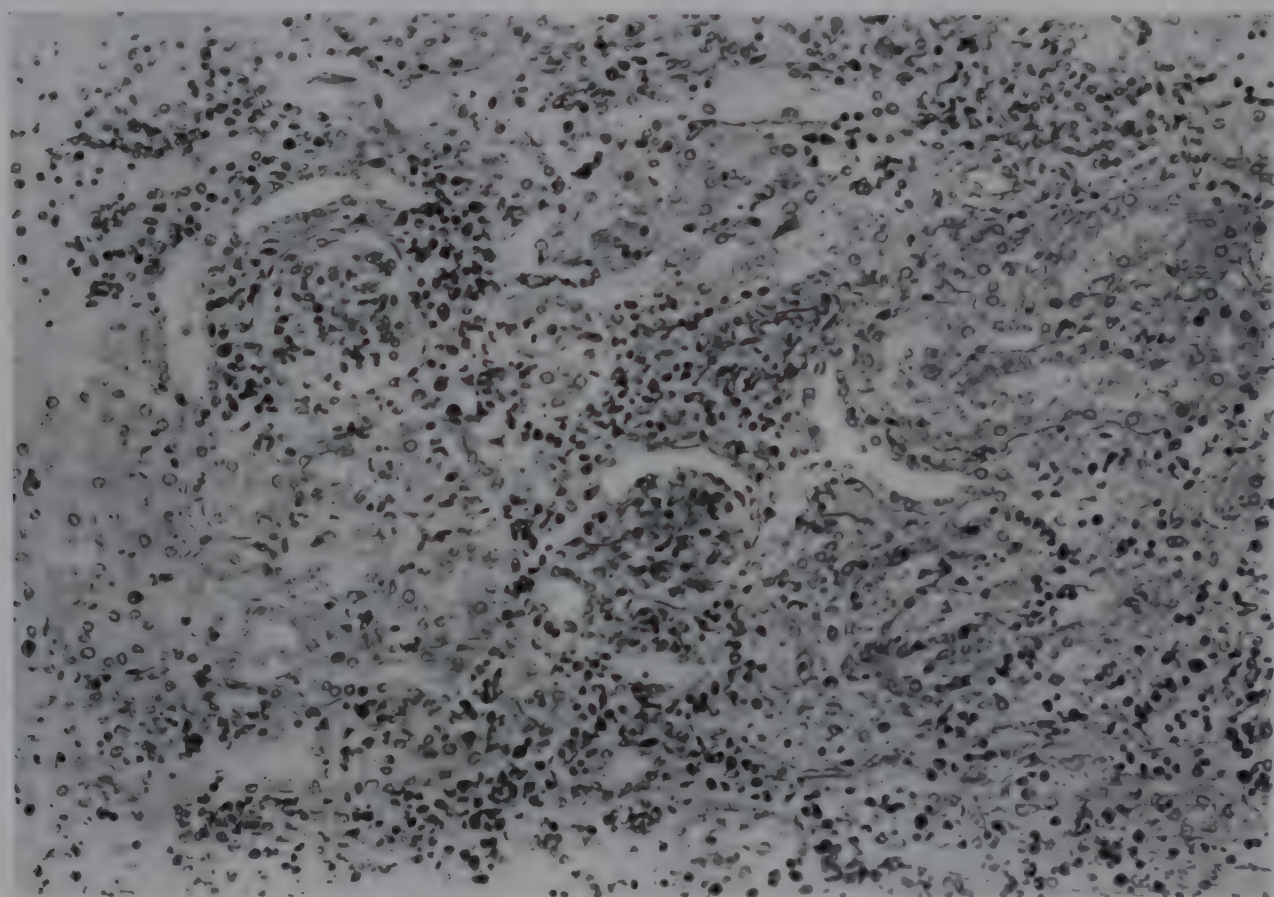


Fig. 114. Acute interstitial nonsuppurative nephritis in scarlet fever.

yellow membrane. The mucous membrane of the pharynx, uvula, and soft palate, and to a less extent of the entire buccal cavity, is red and swollen, with a few scattered petechiae. The papillae of the tongue are prominent. The pharyngeal surfaces may be covered by thick mucus. The epithelium of all these structures is edematous, and leukocytes are present between cells. In the submucosa there are edema, hyperemia, and infiltration with leukocytes. The lymphatics are dilated. Rarely there are small abscesses in the submucosal lymphoid tissue (Pearce). In the deeper connective tissue and muscles of the neck there are frequently small, perivenous accumulations of mononuclear cells. The cervical lymph nodes are enlarged, and unless sup-

the dermis, especially in the papillae. Throughout both the dermis and epidermis are a few polymorphonuclear leukocytes. The cells of the stratum lucidum are edematous, and there are numerous mitoses in the basal cells (Pearce).

Visceral Lesions. Lesions of the viscera are most constant and conspicuous in the heart, liver, kidneys, adrenals, and spleen. In over 90 per cent of cases the heart shows a diffuse interstitial myocarditis, a perivascular infiltration, or a subendocardial infiltration. In all types the chief cell is the lymphocyte. The liver is slightly enlarged and hyperemic. Microscopically demonstrable changes include central necrosis, focal necrosis, and infiltration of the portal spaces by lymphocytes. The

typical lesion of the kidney is an acute interstitial nonsuppurative nephritis (Fig. 114). The kidneys are slightly to moderately enlarged and are mottled gray-red. In the subcortical zones and about the blood vessels there is an irregular infiltration with lymphocytes, mononuclear cells, and plasma cells. There is an associated degeneration of the tubular epithelium, but only minimal changes in the glomeruli (Councilman). In patients dying after several months, an acute glomerulonephritis may be present. The relation of this to scarlet fever is discussed in the chapter on nephritis (p. 746). The adrenals are hyperemic, and about the central vein there are petechiae and infiltration with lymphocytes. The spleen is moderately enlarged. The red pulp is hyperemic, and there are a few leukocytes in the sinuses and cords. The malpighian bodies are conspicuous. The centers are hyperplastic and occasionally necrotic. There is a prominent infiltration of lymphocytes into the subendothelial tissues of the splenic vein and adjacent trabeculae. The thymus is edematous and hyperemic. The lymph nodes generally are enlarged and show reticular hyperplasia (Brody and Smith). Although streptococci occasionally can be isolated from all of the tissues, correlated bacteriologic and histologic studies indicate that the visceral lesions of scarlet fever are caused by the toxin and not by direct bacterial action.

In addition to the pathologic changes outlined in the preceding paragraphs which are an integral part of scarlet fever, other lesions better thought of as complications are caused by the streptococcus. The more important of these are ulcerative pharyngitis, cellulitis of the floor of the mouth and of the neck, suppurative sinusitis and otitis media, suppuration of the cervical lymph nodes, and bronchopneumonia, usually interstitial in type. Rheumatic fever and chorea occasionally follow scarlet fever, but a cause-and-effect relation has not been proved.

Incidence. Transmission. Scarlet fever today is a disease of children between the ages of five and fifteen. Active immunization with the Dick toxin has decreased both the morbidity and the mortality. In 1910 as many as 10 per cent of the attendants in contagious disease hospitals contracted scarlet fever annually. Immunization reduces this figure to less than 1 per cent. The streptococci are usu-

ally acquired through inspired air, but occasionally erythrogenic streptococci are acquired from contaminated milk.

Clinicopathologic Correlation. The incubation period is two to six days, and infectiousness may continue for as long as three to five weeks. After the eighth to the fifteenth day antitoxin can be demonstrated in the blood. The streptococcus invades the blood only after the third day. The prognosis is good in uncomplicated scarlet fever, and most deaths are caused by some complication. A persistently positive blood culture is a bad prognostic sign (Gunn and Griffith).

Scarlet Fever without a Rash. Frequently one child in a family may have scarlet fever and the rest of the family only a sore throat. Those with the sore throats have no rash because their blood contains adequate antitoxin, but they are capable of transmitting scarlet fever. The different strains of streptococci are associated with differing incidence of scarlet fever (Hamburger, Hilles, Hamburger, Johnson, and Wallin).

Surgical and Puerperal Scarlet Fever and Scarlet Fever Following Burns. The pathologic changes in all of these are the same as in the pharyngeal type. The only difference is in the location of the primary streptococcal infection.

Diphtheria

Diphtheria is an infectious disease characterized by a local inflammation at the portal of entry and a systemic toxemia caused by absorption of a powerful exotoxin formed by the bacterium. The usual site of the local inflammation is the pharynx (faucial diphtheria). Less common forms in the respiratory tract are nasal and laryngeal diphtheria. Ocular, aural, cutaneous, genital (prepuce, vulvar, or vaginal), and esophageal diphtheria are rare. Pathologic changes are the same in all forms.

The Local Lesion. In the first twenty-four hours before the membrane forms, the tissues of the tonsillar pillars and the tonsils are swollen, deep red, and project into the lumen. After twenty-four to forty-eight hours a gray, dirty, adherent membrane forms over the surface of the involved region (Fig. 113, p. 206). When the membrane is elevated from the surface, vessels are torn and there is

hemorrhage. Microscopic study shows necrosis of a part or all of the epithelial surface and the formation of a thick membrane of fibrin over the surface. The epithelial cells, which are preserved, are large and frequently multinucleated. In the membrane and in the adjacent living tissue there is a slight to moderate infiltration with lymphocytes and polymorphonuclear leukocytes. The membrane extends over the orifices of the mucous glands, but does not usually penetrate into them. The adjacent skeletal muscle is swollen, and there is hyalinization of the fibers and edema of the

animals by injection of the toxin. A bronchopneumonia caused by streptococci or pneumococci is a common complication in fatal cases. The spleen is enlarged. The malpighian bodies are prominent. There is hyperplasia and necrosis of the centers of the follicles. Changes in the liver are inconspicuous. Studies in animals show depletion of hepatic glycogen, decreased glycogenesis, and decreased rate of disappearance of lactate from the blood in diphtherial intoxication (Holmes). The kidneys are usually slightly enlarged, and are hyperemic and soft. Microscopic examination

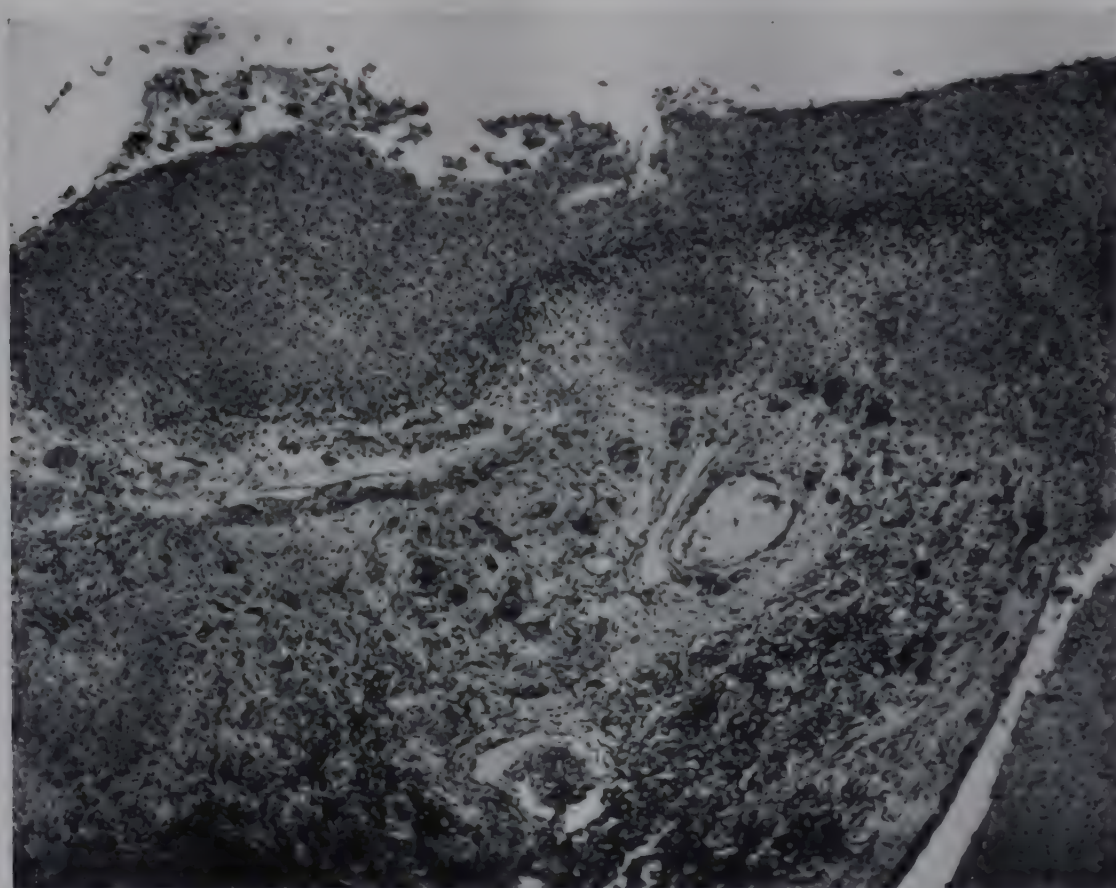


Fig. 115. Diphtheria of tonsil.

interstitial tissue. There are swelling and proliferation of the endothelial and adventitial cells of the capillaries. The blood vessels and lymph vessels are dilated. Bacilli are distributed diffusely or focally through the membrane, and to a less extent in the adjacent necrotic tissue. They are not found in living tissue. Many other bacterial forms, cocci, and bacilli are usually present, but in any one region the greater the number of diphtheria bacilli the fewer the other bacteria (Councilman, Mallory, and Pearce).

Systemic Lesions. The heart is dilated and the myocardium is pale and flabby. The usual lesions are cloudy swelling, fatty degeneration, hyalinization of fibers and interstitial inflammation. Rarely there is necrosis (Gore). Similar lesions may be produced in experimental

reveals cloudy swelling, fatty degeneration, and necrosis of the tubular epithelium or an acute interstitial nonsuppurative nephritis (see section on scarlet fever). The lymph nodes generally, and especially those draining the focal lesion, are soft. Microscopically demonstrable changes include hyperemia, edema, focal necrosis, and hyperplasia of the reticulum cells. Lesions of the peripheral nerves are degeneration of myelin and swelling of the axis cylinders. The bone marrow shows a slight to moderate hyperplasia of both myeloid and erythroid elements. In sharp contrast with diphtherial intoxication in guinea pigs, the adrenals in man are grossly normal, but microscopic studies show small foci of necrosis and hemorrhage (Edmunds and Johnston).

Causal Agent. The bacteriologic diagnosis of diphtheria depends on the identification of characteristic bacteria in direct smears of the exudate and in cultures. Bacteria are rarely found in any tissues except at the portal of entry, but isolated reports of recovery from the blood and internal viscera have been made. Virulence may be checked by subcutaneous injection of broth cultures into guinea pigs. An animal not protected with antitoxin dies in two to five days, and autopsy reveals a serosanguineous inflammation at the site of

out the appearance of manifest disease. Tonsillectomy will eradicate the focus of disease in many carriers, and it appears that children who have had a tonsillectomy develop diphtheria less frequently than other children (Maxcy, Phair, and Smith).

Clinicopathologic Correlation. Diphtheria is rare during the first year of life. The disease reaches a peak incidence between the second and fifth years, decreases in frequency slowly between the fifth and tenth years, rapidly between the tenth and fifteenth years, and is an



Fig. 116. Degeneration of the fibers and infiltration of cells in the heart of diphtheria.

injection, hyperemia and hemorrhage in the adrenal gland, and a hemorrhagic pleurisy. At least two serologic types, based on agglutination, are recognized.

Transmission. Carriers. Diphtheria is contracted in over 90 per cent of all instances by direct contact between persons. The source is either a diseased person or a carrier. There is some evidence that the bacilli may survive in the dust of a room for some hours or days. Casual contact is generally not adequate for transfer of the bacilli, and close personal approximation is necessary.

Carriers are responsible for the persistence of the disease in a community. The carrier state results from the survival of bacilli in the throat or nose after clinical cure, or from acquisition of them from another person with-

unusual disease after the age of fifteen. Susceptibility may be determined with a Schick test. One-thirtieth unit of antitoxin per cubic centimeter of blood serum is sufficient to confer immunity. The severity of the symptoms and the mortality in patients treated with antitoxin vary with the type (McLeod). The mortality varies from place to place and from year to year, and has reached 75 per cent in the more severe and toxic forms of the disease.

The incubation period is one to three days and the course without treatment runs for ten to twenty days. The signs and symptoms depend on local inflammation and systemic effects of the exotoxin. The local membranous inflammation with swelling of the tissues is responsible for soreness, obstruction, and dysphagia in faucial diphtheria, and dyspnea in

laryngeal diphtheria. The systemic manifestations of infection are fever, lassitude, and slight leukocytosis. The degenerative lesions in the kidney are related to the albuminuria. Paralysis, usually late, is caused by the effect of the toxin on the peripheral nerves. Lesions of the heart lead to rapid pulse, arrhythmia, and rarely to sudden circulatory collapse and death. The occasional disturbance in carbohydrate metabolism, glycosuria and low fasting blood sugar, is probably a reflection of hepatic damage, or possibly of the lesions of the adrenal (Holmes).

Special Types of Diphtheria. *Laryngeal Diphtheria.* *Croup.* Croup is a clinical syndrome caused by obstruction to the entrance of air into the lungs as a result of any acute inflammation of the larynx. It is characterized by respiratory stridor, hoarseness or aphonia, and cyanosis or pallor. In recent years, laryngeal diphtheria has become a rare although still serious disease (Gilbert, Meyersburg, and Silverberg).

Esophageal Diphtheria. Involvement of the esophagus is usually an extension from the pharynx. There are numerous small ulcers in the mucosa (Councilman, Mallory, and Pearce).

Nasal Diphtheria. In contrast with faucial diphtheria, nasal diphtheria is frequently mild, and there are few toxemic symptoms, hence patients with the disease are a grave menace to others about them.

Genital Diphtheria. Diphtheria of the vulva, vagina, or prepuce is usually a complication of faucial diphtheria, and represents transfer of the bacilli by the hands or by fomites (Wallfield and Litvak; Berry).

Cutaneous Diphtheria and Wound Diphtheria. Wounds or lesions of the skin may become primarily or secondarily infected with *Corynebacterium diphtheriae*. The pathologic changes and the toxic effects on the viscera are similar to those of faucial diphtheria. Bacteriologic culture of a diphtheria-like organism should be confirmed by virulence tests before a definite diagnosis is made, as avirulent diphtheria bacilli and diphtheroid bacilli are frequently recovered from normal skin and from wounds (Tauber and Goldman).

Aural Diphtheria. The inflammation may spread from the pharynx through the eustachian tube to the middle ear, or diphtheria may be primary in the skin of the external

canal and invade inward through the tympanic membrane. Most examples of postdiphtheritic otitis media are caused by streptococci and not by the diphtheria bacillus.

Diphtheritic Meningitis. Extremely rarely diphtheria bacilli reach the meninges through the blood or by way of the middle ear, and cause a suppurative leptomeningitis (Kalbfleisch).

Acute Fulminating Laryngotracheobronchitis

In young children, usually less than two years of age, the streptococcus produces a characteristic clinical disease characterized by intense inflammation of the larynx, trachea, and bronchi. There are an extensive and advanced edema and inflammation of the mucosa, which may proceed to almost complete occlusion of the lumen. The surface is in many places necrotic, with the formation of ulcers covered by a fibrinopurulent exudate. The smaller bronchi are filled with a purulent exudate. Microscopically throughout the submucosa intense edema and infiltration with polymorphonuclear leukocytes are seen. In the lung there is inflammation of the peribronchiolar tissues, but only a limited inflammation of the surrounding alveoli.

In most instances *Streptococcus haemolyticus* can be recovered in pure culture, but in a few there are admixed staphylococci and pneumococci. It is probable that the ulceration and purulent exudation in the more severe cases are caused by the staphylococcus (Richards). It is possible that at least in some instances the bacterial infection is secondary to that of the influenza virus.

The edema of the larynx leads to respiratory embarrassment and stridor, which requires intubation or tracheotomy. Similarly, the purulent exudate in all of the smaller bronchi induces dyspnea and cyanosis. The course of the disease is fulminating, and the average mortality is about 35 per cent (Neffson).

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XXII

Leptomeningitis. Meningococcal Infections

Leptomeningitis

The term "meningitis" means "inflammation of the meninges." There are two types: pachymeningitis, an inflammation of the dura mater, and leptomeningitis, an inflammation of the pia-arachnoid. In general, meningitis is a term used synonymously with leptomeningitis, and it is qualified only when the dura is involved.

Pathologic Anatomy. In all types of leptomeningitis the brain is swollen, the convolutions are flattened, and the sulci are narrow. The smaller blood vessels coursing in the sub-

as an isolated disease within the cranial cavity, or it may be associated with encephalitis, pachymeningitis, abscess of the brain, or thrombophlebitis of the dural sinuses. In this discussion attention will largely be confined to meningitis as a single disease.

Causal Factors. There is hardly a bacterium that at one time or another has not been reported as the causal agent in acute leptomeningitis. On the basis of over 2700 cases seen by the New York City Department of Health, Neal, Jackson, and Appelbaum report six organisms as the most important (Table 8).

TABLE 8. BACTERIAL CAUSES OF ACUTE LEPTOMENINGITIS

Bacterium	Cases	Percentage
<i>Neisseria intracellularis</i>	1216	44
<i>Mycobacterium tuberculosis</i>	961	35
<i>Diplococcus pneumoniae</i>	209	7
<i>Streptococcus</i>	203	7
<i>Haemophilus influenzae</i>	111	4
<i>Staphylococcus</i>	27	1

arachnoidal space are dilated and filled with blood. The brain substance is indistinctly seen through the pia-arachnoid, because of accumulation of an exudate in this space. The exudate may be slightly cloudy or thick, yellow, and purulent. The distribution of the exudate depends in part on the portal of entry, in part on the size of the subarachnoidal space in various regions, and in part on unknown factors. Thus in a meningitis secondary to disease of the middle ear and mastoid, the exudate is likely to be more abundant under the temporal lobe. In almost all instances the exudate is more abundant at the base, because of the presence of the large cisternal spaces in this region.

Associated Diseases. Meningitis may exist

These figures are perhaps slightly weighted in favor of the meningococcus (*Neisseria intracellularis*) because of the interest of a health department in this disease, in contrast with the other types which are not contagious in the usual sense. In addition to these six common bacteria, there are isolated reports of recovery of *Eberthella typhi* (Hageman), *Micrococcus tetragenus* (McGowan and Kisner), *Neisseria gonorrhoeae* (Branham, Mitchell, and Brainin), *Listerella monocytogenes* (Burn), various members of the colon group (Neal), various members of the salmonella group (Bahrenburg and Ecker), *Pseudomonas aeruginosa* (Evans), *Brucella* (Poston and Thomason), and *Pasteurella pestis* (Myer, Connor, Smyth, and Eddie). In most cases the

organisms produce the typical extracranial disease, but any of them may cause an apparently primary meningitis.

In addition to bacteria, meningitis may be caused by fungi. The most important fungus is the *Cryptococcus* (Johns and Attaway), and less important ones are *Aspergillus* (Linck) and *Actinomyces* (Kramer and Som). The only virus known to produce a meningitis without encephalitis is the virus of lymphocytic choriomeningitis, and even that is questionable (Scott and Rivers). All other types of viral inflammation of the central nervous system are a combination of encephalitis and meningitis, such as encephalitis Type B and equine encephalomyelitis. Rarely metazoan parasites, notably *Ascaris lumbrici-*

brain and spinal cord are contained within a bone case that is perforated for the egress and ingress of blood vessels, lymphatics, and nerves. It follows that any bacterial inflammation must gain entrance to the brain or spinal cord through one of these normal pathways or through some pathologic destruction of the bony case or through a congenital anomaly.

Congenital Anomalies. Spina Bifida and Meningomyelocele. In this condition there is a failure of fusion of the lamina of the vertebral column with a projection of the meninges and spinal cord into the subcutaneous tissues of the back (see the section on spina bifida in the chapter on diseases of the nervous system, p. 941). Thus the cerebrospinal fluid is in close contact with the surface of the body

TABLE 9. BACTERIAL CAUSES OF ACUTE LEPTOMENINGITIS IN CHILDREN

Bacterium	Cases	Percentage
<i>Mycobacterium tuberculosis</i>	290	41
<i>Neisseria intracellularis</i>	160	23
<i>Hemophilus influenzae</i>	78	11
<i>Streptococcus</i>	69	10
<i>Diplococcus pneumoniae</i>	69	10
All others	39	5

coides, invade the meninges and set up a mild inflammatory reaction. Finally there is a group of meningitides from which no living agent can be isolated. These are usually termed “aseptic meningitis” or “Wallgren’s aseptic meningitis” (Baird and Rivers).

Relation of Age to Cause. The causal agent of acute meningitis in part depends on the age of the patient. In contrast with the figures quoted for all ages are those in Table 9, based on 705 patients seen at the Boston Children’s Hospital. These figures are of course influenced by the fact that all of the patients were hospitalized.

Meningitis in the Newborn. The most common bacterial cause of meningitis in the newborn is *Escherichia coli*. The portal of entry in some cases is an inflammation of the middle ear and in others an inflammation of the umbilicus or a bronchopneumonia. The normal habitat of the colon bacillus suggests contamination in the birth canal or from bath water.

Associated Lesions. Predisposing and Contributing Factors. Pathways of Infection. The

and bacterial invasion is not uncommon. About 20 per cent of newborn infants with this condition die of meningitis (Russell and Donald). A closely related condition is the pilonidal cyst with an occult spina bifida. Here there is a sinus tract lined with epithelium that may penetrate to the dura, and a pathway for infection of the meninges is available (Walker and Bucy).

Trauma. It is immediately apparent that penetrating wounds of the skull and of the vertebral column serve as an ideal path for the direct introduction of environmental bacteria into the meninges. This represents a serious problem in wartime neurologic surgery. Of far greater importance in this category is the possible effect of lumbar puncture. In most persons, following lumbar puncture there is slight headache for a few hours, and if the puncture is repeated during this period of time, there are an increased protein content and a pleocytosis of lymphocytes in the spinal fluid (Reynolds and Wilson). If the technique is faulty, bacteria may be introduced by the needle or contained within solutions, such as

local anesthetics (Shrewsbury). About one-half the cases of meningitis following lumbar puncture are caused by *Pseudomonas aeruginosa*. In cats and rabbits bacteria injected into the blood do not localize in the meninges un-

Metastases. Bacteria in the blood stream, with or without some primary lesion in other viscera, may localize in the leptomeninges and set up a meningitis. The meningococcus rarely localizes and produces lesions in any other



Fig. 117. Acute leptomeningitis.



Fig. 118. Bulging of anterior fontanelle in acute leptomeningitis. (Photograph by courtesy of Dr. Theo. Walsh.)

less cerebrospinal fluid is withdrawn immediately before the injection. This indicates that meningitis may follow lumbar puncture when there is a septicemia (Weed, Wegforth, Ayer, and Felton).

organ. With other bacteria localization in the meninges is a secondary process, and the factors which control it are not entirely understood. The most important of these are the pneumococcus in association with lobar pneu-

monia, the streptococcus in association with bronchopneumonia and other lesions, and the staphylococcus in association with furunculosis and osteomyelitis. Rarely these same organisms produce a meningitis without demonstrable changes in any other part of the body.

Infections of the Nose, Nasal Sinuses, and Pharynx. Aside from meningococcal meningitis and the hematogenous meningitides just described, the most important associated

Infections of the Ear, Mastoid, and Pneumatized Petrosal Bone. The situation here is much the same as with the nose and paranasal sinuses. Infection enters the cranial cavity through a pathologic or congenital dehiscence of bone, through lymphatics, or through blood vessels. The ear is more important than the nose in the relation of meningitis to infections about the head (see chapter on otitis media, p. 263).

TABLE 10. RELATION OF ASSOCIATED LESION TO BACTERIAL CAUSE OF MENINGITIS

Associated Lesion	Streptococcus	Diplococcus pneumoniae	Haemophilus influenzae	Staphylococcus
Disease of the ear	121	75	20	7
Pneumonia	1	27	15	4
Infection of upper respiratory tract	8	12	4	0
Injury to the head and skull	8	8	4	1
Operation on the head, nose, or throat	3	4	0	0
Wounds, abscesses, and furuncles	3	0	0	2
No evidence of a primary lesion	33	50	48	4

lesions are infections of the nose, nasal sinuses, pharynx, middle and internal ears, mastoid, and a pneumatized petrous bone. The nose and nasal sinuses are closely connected by nerves, lymphatics, and blood vessels with the inside of the cranial cavity. In addition, some of the sinuses are separated from the dura by only a thin plate of bone. Thus a suppurative inflammation may penetrate to the leptomeninges through osteomyelitic destruction of

Infections of the Eyes and Face. The veins draining the periorbital tissue, the sides of the nose, and to some extent the subcutaneous tissues of the cheek, penetrate into the cranial cavity and empty into the cavernous sinus. Bacterial infections in these regions may lead to thrombophlebitis of the cavernous sinus and secondary leptomeningitis. The well recognized danger of furunculosis on the nose is based on this fact.

TABLE 11. RELATION OF ASSOCIATED LESION TO TYPE OF PNEUMOCOCCUS IN MENINGITIS

Associated Lesion	Type I	Type II	Type III	Group IV
Disease of the ear	6	7	35	11
Pneumonia and respiratory infection	13	7	5	14
No evidence of primary lesion	10	5	6	13

bone, by passage of the bacteria along the lymphatics about the nerves and vessels, and by blood vessels that drain into the dural sinuses. The lymphatics about the nerves are especially important, since they empty directly into the subarachnoidal space. In addition two cases have been reported in which infection traveled along a congenital defect in the bony wall separating the sinuses from the cranium, and along a persistent craniopharyngeal pouch of Rathke (Mayer).

Relation of the Associated Lesion to the Bacterial Cause. The particular bacterium responsible for a given case of meningitis in part depends on the associated lesion, as shown in Table 10, taken from the studies of Neal, Jackson, and Appelbaum. In this study, of 150 streptococci, 141 were hemolytic. Of the pneumococci, 161 were typed, with the result shown in Table 11.

General Clinicopathologic Correlation. Broadly speaking, the signs and symptoms of

meningitis are caused, first, by infection, and, second, by increased intracranial pressure. The symptoms of infection are fever, chill, headache, and malaise. The general symptoms and signs of an increase of intracranial pressure are headache, vomiting, and choked disk. The specific signs of the inflammation in the leptomeninges are stiff neck, exaggerated reflexes, and a positive Kernig sign.

Complications and Sequelae. The most serious complication of an acute meningitis is organization of the exudate, blocking partially or totally the flow of the cerebrospinal fluid. If the organization occurs at the base, about the foramina of Magendie and Luschka, the passage of fluid from the ventricles to the subarachnoid space is completely blocked, and there results a noncommunicating internal hydrocephalus. Most instances of hydrocephalus in young children result from this type of lesion. If the organization completely surrounds the great basal cisterns, a type of communicating hydrocephalus is produced in which the fluid can escape into the spinal arachnoid but not into the cerebral arachnoid, and thus the absorbing power of the cerebral arachnoidal granulations, representing about 75 per cent of the total, is lost (Dandy and Blackfan). During the course of a meningitis there may be transient loss of the activity of one or more of the cerebral nerves, most commonly the optic or auditory, but only occasionally is there permanent loss of function. On the other hand the bacteria, especially the meningococcus, may invade the tissues of the eye or of the internal ear, and produce a peripheral blindness or deafness.

Meningococcal Infections

The meningococcus was first identified in the cerebrospinal fluid in meningitis, and the laity has come to associate the two very closely. This is unfortunate, because the meningococcus causes other lesions, and there is even some evidence that the real disease for which it is responsible is a rhinopharyngitis. From a clinical and pathologic standpoint, there are four disease entities: (1) acute meningococcal meningitis; (2) chronic basilar meningitis; (3) acute meningococcemia; and (4) chronic meningococcemia.

Acute Meningococcal Meningitis. The most obvious pathologic alteration during the first

to third day is the lesion of the skin, varying from simple petechiae or ecchymoses to maculopapular nodules up to 2 cm. in diameter. The essential change in each is hemorrhage into the dermis or subcutaneous tissue. In addition, there are hyperemia of the dermal vessels, thrombi in some vessels, and a nodular infiltration with leukocytes (Hill and Kinney). Cocci are present in the dermal lesions (Tompkins). After a few days, the extravasated red cells are phagocytized and each spot becomes less firm and is rusty brown. Similar lesions are occasionally present in the mucous membrane and in the synovia of the joints. Changes within the cranial cavity and spinal canal are variable and depend on the duration and severity of the disease. In the fulminating types, there may be no grossly demonstrable change in the meninges or brain. At the most, there is an increase of fluid in the subarachnoid space and flattening of the convolutions. In microscopic sections, a few leukocytes are seen. In the usual case, running a course of six to ten days, the vessels of the dura mater are prominent, and there are rare petechiae in the membrane. The pial vessels are hyperemic and petechiae are more numerous. In the subarachnoid space there is an exudate which either fills the sulci or completely covers the sulci and convolutions. The exudate is composed predominantly of fibrin and polymorphonuclear leukocytes. The ependymal cells are swollen and vacuolated. In severe infections the exudate extends into the brain along the perivascular lymphatics.

Rarely the inflammation extends from the meninges into the brain and there is an acute necrotizing purulent encephalomyelitis (Wartman and Hanger).

Important complications include a necrotizing myocarditis (Holman and Angevine) and purulent arthritis (Boger).

In most fatal cases, and in some patients who recover, there is an upper or lower respiratory infection with bronchitis, bronchopneumonia, lobar pneumonia, or multiple abscesses of the lung. The meningococcus can frequently be isolated from these tissues, but it is probable that the pathologic changes are caused by associated streptococci and pneumococci. The spleen is moderately enlarged and softened. The white pulp is prominent and hyperplastic, and the red pulp is hyperemic. The bone marrow shows myeloid hyperplasia.

Purulent conjunctivitis early, and a panophthalmitis late, occur in 2 to 5 per cent of the patients. Spread of the infection to the labyrinth with suppuration of the cochlear tissues is the usual cause of postmeningitic deafness.

Clinicopathologic Correlation. Correlation of the pathologic changes and clinical signs and symptoms in meningococcal meningitis is most accurate if three stages are recognized:

irregularities, slowing of respiration, exaggeration of the reflexes, and dulling of the senses with coma. A relapse after a period of relative good health for six weeks occurs in 2 to 5 per cent of cases.

The mortality varies with the epidemic and country. In New York in 1904–1905, the mortality was 73 per cent (Flexner). After introduction of the antiserum, the mortality



Fig. 119. Ecchymoses in skin in acute meningococcemia. (Armed Forces Institute of Pathology, Neg. No. 75426.)

a stage of local inflammation, a stage of sepsis, and a stage of meningitis. In the first stage, lasting two to four days, there is an inflammation of the nasopharynx and the signs and symptoms are those of a coryza: conjunctivitis, pharyngitis, sinusitis, and tonsillitis. With invasion of the blood, there are the general symptoms of bacteremia—fever, chills, rapid pulse, and leukocytosis—plus those of capillary fragility and hemorrhage—rash on the skin and arthralgia. After about forty-eight hours, the inflammation of the meninges begins, and there are then the signs of increased intracranial pressure and cerebral irritation or depression: slowing of the pulse with vagal

averaged 30 per cent (Flexner). With the use of the sulfonamide drugs, the mortality in the epidemic of 1942–1943 in the United States was not over 5 per cent.

Chronic Basilar Meningitis. In a few patients the exudate at the base of the brain does not resolve but organizes. There are proliferation of fibroblasts and capillary vessels, and encapsulation of small locules of pus. The exudate blocks the foramina of the fourth ventricle and partially fills the basal cisterns. The ventricular system is dilated and the brain is compressed and atrophic. The prognosis is poor.

Acute Meningococcemia. In a small num-

ber of persons, infection with the meningococcus is predominantly a septicemia, with a sudden onset of malaise and abdominal pain. Within twelve to twenty-four hours there are cyanosis, many petechiae over the trunk and extremities, and a general clinical picture of collapse. The meningococcus is present in large numbers in the blood stream. Pathologic change include petechiae and ecchymoses in the skin and many internal tissues and usually massive hemorrhage in the adrenals (Martland). There is as a rule no inflammation, or only a very slight inflammation of the meninges (Herbut and Manges). This syndrome is known as the "Waterhouse-Friderichsen syndrome." It has been postulated that death results from the adrenal hemorrhage but most evidence points to overwhelming infection.

Chronic Meningococcemia. In a small percentage of patients with meningococcal infections, the bacteria enter the blood, but do not localize in the meninges. In another small percentage there is a meningitis, but either bacteria never leave the blood, or they reenter it after two to three weeks. These two groups together constitute chronic meningococcemia. It is characterized clinically by sudden onset with intermittent fever and chills, maculopapular rash, myalgia and arthralgia, leukocytosis, a positive blood culture, and a variable duration of one to thirty weeks. The mortality is about 15 per cent. In fatal cases, half show a meningitis, and half have an acute or subacute vegetative endocarditis (Master). Changes in the other viscera are those of infection: hyperplasia of the spleen and lymph nodes, and degenerative lesions of the viscera.

Causal Agent. *Neisseria intracellularis* is present in the skin lesions, in the nasopharynx, in the blood, and in the cerebrospinal fluid at different stages of the disease. After death, the bacteria rapidly die, and all cultures should be made within twelve hours after death. Agglutinins are present in the blood in only 50 per cent of patients and then in low dilution. An endotoxin is lethal for animals. In sections of tissue, the cocci are predominantly intracellular.

Incidence. Meningococcal infections are most common in children and young adults, in the winter and spring, in people of lower economic groups, and in armies. It is estimated that only 0.01 to 3 per cent of the ex-

posed population develop meningitis during an epidemic.

Transmission and Pathogenesis. The meningococci enter the body through the upper respiratory tract, and cultures of the nasopharynx during an inter-epidemic period will show that 2 to 4 per cent of all people harbor the meningococcus in the posterior nasopharynx. Some of these are temporary and others chronic carriers. If the carrier rate goes over 20 per cent, an epidemic is probable (Muel-ler). During an epidemic, the carrier rate may reach 80 per cent. In the nasopharynx there is a mild inflammation and humoral antibodies may be present in the blood. After the cocci are transferred as an air-borne infection from a carrier to the nasopharynx of a susceptible host, they invade the blood and localize in the meninges. The sulfonamide drugs have proved useful in control of carriers (Kuhns, Nelson, Feldman, and Kuhn).

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XXIII

Diseases Caused by Bacteria of the Genus Hemophilus

The first bacterium of this genus to be isolated and identified was *Hemophilus influenzae*, cultured by Pfeiffer from the nasopharyngeal secretions of patients with influenza. Subsequent studies showed that a virus is the cause of influenza, but the influenza bacillus is important as the etiologic agent of a type of meningitis and of tracheobronchitis. Another member of the genus is the causal agent of whooping cough.

Whooping Cough

Although there has been considerable discussion and dispute concerning the causal role of *Hemophilus pertussis* in whooping cough, the bacteriologic, serologic, and experimental evidence accumulated in the last two decades leaves little doubt that there is a positive and clear relation.

Pathologic Anatomy. The most distinctive and characteristic lesion of pertussis is an inflammation of the walls of the bronchi and bronchioles, and to a less extent of the trachea and nasopharyngeal mucosa. The mucosa of the upper and lower respiratory tract is swollen and red, and is covered by a mucopurulent exudate. Microscopically numerous bacilli are seen to be entangled in the cilia of the moderately well preserved columnar ciliated epithelial cells. The midzonal and basal layers of the epithelium are necrotic and are infiltrated with polymorphonuclear leukocytes and mononuclear cells. Occasional epithelial cells are in the process of mitosis. In the adjacent connective tissue there is infiltration with polymorphonuclear leukocytes and mononuclear cells, with the formation of small abscesses. The epithelium may be elevated from the basement membrane by the exudate, and may show early changes of necrosis (Gallavan and Goodpasture; L. W. Smith).

The relation of whooping cough to pneumonia is difficult to determine. In almost all fatal cases and in a few patients who recover there is definite bronchopneumonia. In most cases, radiographic examination will show a peribronchiolar thickening. In some instances at autopsy it is possible to demonstrate bacilli in the alveolar exudate, which is made up of many leukocytes and a little fibrin, and may show striking necrosis (Wollstein). In these examples there can be little doubt that the pneumonia is directly related to the specific bacterium. On the other hand most pneumonias in patients with whooping cough are either a typical bronchopneumonia or an interstitial bronchopneumonia similar to that seen in association with other infectious diseases such as measles and influenza. Rarely inclusion bodies are present in the epithelial cells (McCordock and Smith).

Throughout many tissues there are small or large hemorrhages, especially in the serous membranes and in the brain and leptomeninges. Occasionally there are larger hemorrhages into the muscles of the abdominal wall (Lasch). There is not infrequently edema of the face and neck, and rarely there is anasarca. Rarer complications directly related to the acute phase of whooping cough are dilatation of the heart (Thompson), subcutaneous emphysema (Worden and Chaisson), and fracture of the ribs (Swineford and McKinnon). In the brain there are, in most fatal cases, small foci of hemorrhage, and occasionally there is an encephalitis of the postinfectious type (Nelson).

In some children the secondary infection of the bronchi and of the lungs becomes chronic, and at autopsy these show bronchiectasis, intense emphysema, and hypertrophy and dilatation of the right ventricle. It is highly probable that some examples of bron-

chiectasis in adults are based on an attack of whooping cough during childhood.

Causal Agent. Immunity. *Hemophilus pertussis* may be isolated on properly prepared media, either on so-called "cough plates" (Gardner and Leslie) or from the lung at autopsy. Complement binding bodies and agglutinins appear in the serum during the disease or after vaccination. Convalescent and hyperimmune serum is said to be of value if given before the paroxysmal stage (Sauer). On special media, an endotoxin is developed, which may be used in a skin test for the determination of the immune state (Thompson).

Typical pertussis has been produced in human volunteers and in primates by inoculation of pharyngeal washings and virulent cultures. In the chick embryo the bacilli localize in the cilia of the respiratory epithelium (Gallavan and Goodpasture).

Incidence. Whooping cough is almost exclusively a disease of children before the seventh year of life, but it is occasionally seen in adults. A second attack is most unusual (R. E. Smith).

Transmission. The morbidity of whooping cough in susceptible children is directly related to the intimacy and frequency of contact with an active case. Thus, secondary cases are more frequent in families than in schools and institutions (Culotta, Dominick, and Harrison). About 80 per cent of all children fully exposed develop the disease. Carriers exist, but are responsible for only an occasional example of the disease.

Clinicopathologic Correlation. The incubation period varies from three to twenty days, and averages seven days. Organisms disappear from the droplets in the cough by the sixth week in most children (R. E. Smith). The pressure on the chest during the paroxysm probably interferes with the return of blood, and is responsible for the edema and the dilatation of the heart (Thompson). The characteristic increase in the white blood cell count is probably related to a toxic substance of Phase I organisms. Counts may reach as high as 250,000, and average 20,000 to 30,000 (Ch'in). The only report in the literature of lymphoid leukemia following whooping cough was in a child who already had leukemia (Levy, Grand, and Krakauer). An occasional case of myeloid leukemia following whooping cough has been reported (Morris and Hur-

witz). The characteristic irritation of the bronchial tree and the cough are clearly explained by the inflammation of the ciliated cells of the respiratory tract. Convulsions may result from any one of three mechanisms—hemorrhage into the meninges or brain, circulating toxin, or latent tetany (Powers). There is no objective evidence that whooping cough has an unfavorable influence on pulmonary tuberculosis in children (Siegel and Goldberger).

Diseases Caused by Hemophilus Influenzae

In 1892, Pfeiffer isolated a small bacillus from the nasopharyngeal secretions of patients with epidemic influenza, and announced that it was the cause of the disease. The intensive investigation of the pandemic of influenza of 1917–1919 completely disproved the causal role of *Hemophilus influenza* in epidemic influenza, but it was not until 1933 that Smith, Andrewes, and Laidlaw isolated and identified the real cause—a virus. However in the meantime *Hemophilus influenzae* had been isolated from a number of pathologic lesions, notably a definite type of meningitis in children.

Influenzal Leptomeningitis. The lesions in meningitis caused by *Hemophilus influenzae* differ in no essential particular from those found in other forms of purulent meningitis. The brain is hyperemic and edematous, with flattening of the convolutions. The subarachnoidal space is filled with a patchy, yellowish green, thick, purulent exudate, most abundant at the base. The ventricles are distended and contain a turbid or purulent fluid. Microscopically the exudate is seen to consist of fibrin, a large number of polymorphonuclear leukocytes, and a few red blood cells, lymphocytes, and mononuclear cells. In more chronic cases the predominant cell is the mononuclear cell. The adjacent portions of the brain are invaded and in part destroyed by the inflammation. Occasionally there is organization of the exudate.

In about one-half of the cases there is no significant pathologic lesion in the remaining viscera. In the other half there is otitis media, upper respiratory infection, or bronchopneumonia; but not all of these lesions are caused by the influenza bacillus. Until the introduction of specific serum and the sulfonamides, the mortality was above 90 per cent. It is more

common in children in the months from October to December, in contrast with respiratory infection, which reaches its peak after January (Neal, Jackson, and Appelbaum; Rivers). Relapses and resistance to immune serum may be explained by the ingestion of bacilli by phagocytes without destruction of them (Fothergill, Chandler, and Dingle).

Acute Laryngotracheitis with Septicemia. The Type B influenza bacillus is apparently capable of producing in children an acute laryngitis in the absence of the influenza virus. The pharynx is red and swollen, but there is no exudate on the surface and no ulceration.

acute, purulent inflammation of the conjunctiva, occasionally with ulceration, is produced by what is generally known as the Koch-Weeks bacillus. This organism is identical with *Hemophilus influenzae*. Occasionally the inflammation persists as a subacute or chronic purulent conjunctivitis (Guyton).

Hemophilus Influenzae as the Cause of Subacute Bacterial Endocarditis. The typical pathologic picture of subacute bacterial endocarditis may be produced by infection with either *Hemophilus influenzae* (Rose) or *Hemophilus parainfluenzae*. The lesions of the valves and of the endocardium, and the evi-



Fig. 120. Acute leptomeningitis caused by *Hemophilus influenzae*.

The entire larynx, but particularly the epiglottis, is red and markedly edematous, so that tracheotomy is required in about half of the cases. In the lungs there are hyperemia, edema, and focal areas of a hemorrhagic type of bronchopneumonia. *Hemophilus influenzae* Type B may be recovered with regularity from the blood and from the secretions of the upper respiratory tract. The onset is sudden, and there are conspicuous signs of an infection of the pharynx and larynx—sore throat, difficulty in swallowing, cough; and the general systemic reactions of fever, leukocytosis, and prostration. The mortality is high, but recovery sets in after about forty-eight hours. Specific serum is apparently of value (Sinclair).

Acute Contagious Conjunctivitis. A typical

dences of systemic embolism, are identical with those caused by *Streptococcus viridans*. Complicating meningitis is more common than in the streptococcal type (Craven, Poston and Orgain).

Miscellaneous Lesions. Influenzal pyarthrosis occurs with or without influenzal meningitis. There is no destruction of the tissues of the joint, and complete restoration of function is to be expected (Weaver and Sherwood). In a rare example of inflammation of the urinary tract, *Hemophilus influenzae* is present in the urine but pathologic studies are inadequate to establish the causal role of the organism (Burkland and Leadbetter). Suppurative pericarditis is a rare lesion and follows "croup" (Kresky).

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XXIV

Pneumonia

The basic pathologic change in pneumonia is an inflammation of the pulmonary tissue. As a primary cause of death pneumonia ranks third in the United States, and is exceeded only by heart disease and cancer. As a contributory cause of illness or death, bronchopneumonia plays a major role in the acute exanthems, in cardiac failure, in cancer, and in many other conditions.

Classification of the Pneumonias. Pneumonias may be classified on the basis of anatomic distribution, type of pathologic change, causal agent, pathogenesis, chronologic sequence, or relation to other disease of the lung or body as a whole. In general, there is a relation between the various groups. For example, lobar pneumonia (anatomic) is usually characterized by an exudate rich in fibrin and leukocytes (pathologic), is caused by the pneumococcus (causal agent), is an acute, self-limiting disease (chronologic), and is rarely related causally to other diseases in the body.

Anatomic Classification. In some types the exudate is largely confined to the interstitial tissue, especially about the bronchi, and the condition is designated *interstitial bronchopneumonia* or *interstitial pneumonitis*. In others the exudate is present in and fills the alveolar spaces. If a large part or all of one or more lobes is involved, the term *lobar pneumonia* is applicable, while if the inflammatory process involves irregular parts, principally spherical foci about the smaller bronchi, or is confined to a lobule, it is customary to use the term *bronchopneumonia* or *lobular pneumonia*.

Classification by Pathologic Change. As in all other inflammations the change may be acute or chronic. In turn the acute varieties may be subclassified on the basis of type of exudate, as *fibrinous* or *croupous pneumonia*, *hemorrhagic pneumonia*, *necrotizing pneumo-*

nia, or *suppurative pneumonia*. Each of these is characteristic of and is related to certain causal agents. Thus fibrinous pneumonia is typical of pneumococcal infections, hemorrhagic pneumonia of streptococcal infections especially those following influenza, necrotizing pneumonia is associated with tularemia and plague, and suppurative pneumonia is seen most frequently in staphylococcal infections. Another approach to the subclassification of the acute pneumonias may be made from the viewpoint of the type of exudative cell: polymorphonuclear leukocytes in pneumococcal, streptococcal, and staphylococcal infections, and mononuclear cells in the pneumonia of tularemia and Q fever. *Chronic pneumonia* or *pneumonitis* may represent the continuation of an acute pneumonia with failure of resolution, or may be primarily a chronic inflammation, as in some fungal and bacterial infections.

Classification in Relation to Pathogenesis. The causal agent may be brought to the lung through the respiratory tract (*aerogenous pneumonia*) or by the blood stream (*embolic* or *hematogenous pneumonia*). An example of the former is pneumococcal lobar pneumonia; of the latter, the pneumonia of tularemia. In some diseases either the aerogenous or the embolic variety may be present. In bubonic plague, for example, a terminal pneumonia may arise as a blood-borne infection, but in pneumonic plague the infection is air-borne.

Classification by Chronologic Sequence. Most pneumonias are acute self-limiting diseases and result in recovery or death in a relatively short period of time. At any one period there is a characteristic pathologic appearance. If resolution fails, the exudate is invaded by fibroblasts and capillaries, and the diagnosis of *organizing pneumonia* is appropriate.

Classification by Causal Agent. From the standpoint of treatment the most useful classification is that based on the cause of the pneumonia. Two great categories are recognized: pneumonia caused by micro-organisms, and pneumonia caused by nonliving chemical substances and particulate matter. Micro-organisms may be divided into the usual categories—bacteria: *Pneumococcus*, *Streptococcus*, *Staphylococcus*, *Klebsiella*, *Salmonella*, *tubercle bacillus*, *Hemophilus*, *Pasteurella tularensis* and *Pasteurella pestis*, and *Corynebacterium diphtheriae*; rickettsiae: *Rickettsia burneti*, of Q fever; viruses: influenza, measles, and ornithosis; fungi: *Coccidioides* and *Blastomyces*; protozoa: *Endamoeba*; and metazoa: the pneumonias associated with the passage of the roundworm and the hookworm through the lung. Chemical substances and particulate matter include gases and atomized liquids, aspirated nose drops and gastric content, and finely divided solids such as silica and other irritating dusts.

Classification in Relation to Other Disease. If a pneumonia occurs in an otherwise healthy person, it is classified as *primary pneumonia*; while if the inflammatory process in the lungs is sequential to some other pathologic lesion in the respiratory tract, it is designated as *secondary pneumonia*. Preexistent or concomitant disease of the lung may influence both the incidence and the severity of pneumonia. Thus in chronic passive hyperemia there is probably a decreased resistance of the pulmonary tissues. Similarly in a debilitated patient who is confined to bed there is inadequate circulation in the posterior parts of the lung, and *hypostatic pneumonia* may be established. During and after anesthesia, and during coma, the cough reflex is abolished. Mucus collects in and obstructs the bronchi, and *postoperative pneumonia* may occur. In injuries to the thoracic wall there is decreased expansion of the lungs, and *post-traumatic pneumonia* may result.

General Pathologic Changes and Clinico-pathological Correlation. It is evident that no single description of the pathologic anatomy and clinical symptoms of pneumonia is possible. However, it is worth while to review some general considerations.

The essential feature is inflammation of the lung, bringing about the accumulation of an exudate of some sort in the tissues and spaces

of the respiratory tract. Air is replaced by exudate.

Changes in Color and Consistency of Tissue. The first step in the differential diagnosis of pneumonia is an evaluation of the color and consistency of the tissue. The fluid of the exudate is blood plasma, and it is a light yellow. The white blood cells are buff. The fibrin is white. Red blood cells in proportion to number contribute a red color, and tissue and cells digested by autolytic enzymes have the yellow color of pus. If the exudate is poor in fibrinogen, the tissues are flabby, and quantities of fluid exude from the cut surface, while if the exudate is rich in fibrinogen the clotted fibrin is firm and the cut surface is dry. Further, the plugs of fibrin in each alveolus spring out from the cut section and give the appearance of a finely or coarsely granular cut surface. So long as the alveolar walls are intact the lung is firm and elastic, but in necrosis the elasticity is lost and the tissue is soft and friable.

In the living patient the clinician evaluates the color and consistency by other methods. The replacement of air and the *consolidation* of the pulmonary tissue alter the physical signs and radiographic appearance. The consolidated lung does not expand on inspiration, hence the thoracic wall will not move as much or as rapidly—*lack of or delay in inspiratory expansion*. On percussion the note is that of solid tissue rather than of air—*impaired or flat percussion note*. Auscultatory sounds are altered since air is not entering and leaving the alveoli at each inspiration. If the exudate is limpid and abundant, air bubbles through the fluid—*bubbling rales*. If the liquid is minimal or viscid, the pulling apart of the respiratory bronchioles at each inspiration elicits a crackling sound—*crackling rales*. If the consolidation is extensive and firm, as in exudates rich in fibrin, the sounds of vesicular breathing are entirely absent and only the rush of air through the major bronchi is heard—*bronchial breathing*. In the radiograph the degree of radiopacity is a direct expression of the density and cellular content of the exudate. Examination of the sputum gives information concerning the exudate and the presence of necrosis. A hemorrhagic exudate, as in the early stages of pneumonococcal lobar pneumonia, is associated with a rusty red sputum. A purulent inflammation, especially in the bronchi, produces a thick yellow sputum. There are few

enzymes in the body that digest elastic fibers, hence their presence in the sputum means that there has been necrosis of tissue.

Involvement of Specific Tissues. The second step in the diagnosis of pneumonia is an evaluation of the tissues involved. Is the exudate predominantly in the bronchioles or bronchiolar walls (interstitial pneumonia) or does it involve the alveolar spaces? In the latter instance, is the consolidation coextensive with an anatomic lobe (lobar pneumonia) or is it irregular (bronchopneumonia)? If the consolidation is irregular, are the foci discrete or confluent (confluent bronchopneumonia)? Is there an associated bronchitis? Is there an associated pleurisy? The existence of inflammation in the walls of the bronchi and the accumulation of exudate in the lumen are synonymous with the clinical symptom of cough. The severity of the cough and the amount and character of the sputum are therefore the basis for a clinical evaluation of the presence and type of an associated bronchitis.

Inflammations of the pleura are of different types, and the clinical manifestations are variable. If the exudate is minimal and fibrinous or serofibrinous, the pleural surfaces are dull and are covered by a gray, dry, granular, easily removable material. The cavity contains a small amount of clear or slightly cloudy fluid. Under these conditions the two pleural surfaces slide roughly on one another. The stimulation of the nerve endings is interpreted in consciousness as *pain*. This experience of pain leads to splinting of the thoracic wall and to an attempt to decrease the excursion of respirations—*short, grunting, rapid respiration*. On the other hand if the exudate is abundant and serous or purulent, the anatomic findings and clinical signs are quite different. The size of each hemithorax is limited, and the excessive amounts of fluid can accumulate in the pleural cavity only at the expense of some other tissue or space. The alveolar space of the homolateral lung is used by collapse of the lung—*compression atelectasis*. The alveolar space of the contralateral lung is made available to a limited extent by a *shift of the mediastinum*. Lowering of the diaphragm and bulging of the soft tissue between the ribs are two other possibilities. The physical signs of a serous or purulent pleurisy are related to these alterations in structure and to the interposition between the thoracic wall and the in-

flamed lung of a layer of fluid. It follows that the thoracic wall does not move with respiration, that the percussion note is dull or flat, and that any sounds produced in the lung are heard faintly.

Associated Disease. The third step in the diagnosis of pneumonia is a search for evidence of preceding or coexistent disease. If some other lesion or disease is present, it must then be determined whether it has a causal relation to the pneumonia, is a complication of the pneumonia, or is an incidental, unrelated condition.

Identification of Cause. This is the fourth and final step in the diagnosis of pneumonia. In chemical pneumonia the history is pertinent. In pneumonia caused by micro-organisms, isolation of pure cultures, demonstration of the organism in the tissue, demonstration of the presence of immune bodies in the blood, and demonstration of antigenic substances in the body fluids and tissues are important.

Bacterial Causes. Aside from the specific pneumonias of plague, tularemia, etc., most primary and secondary inflammations of the lung are caused by the pneumococcus, streptococcus, and staphylococcus (Rumreich, Shaughnessy, Mulcahy, Willett, Kellogg, and Mitchell).

Incidence. The National Health Survey, a medical history of 2,152,741 white persons in the United States in 1934–1936, showed that the annual death rate from pneumonia per thousand living persons was 5.4, with a somewhat higher rate in rural than in urban communities, in men than in women, in infancy and old age than in adulthood, in low-income families than in high, and under crowded living conditions than in well-housed communities (Britten).

Predisposing and Contributing Factors. In addition to the factors such as preceding disease, coma, trauma to the chest, and anesthetics, discussed in preceding passages, there are other predisposing and contributing factors related to the environment and the constitution of the person.

All pneumonias are more common in the fall, winter, and spring, and during periods when there are excessive fluctuations in environmental temperature.

The incidence is higher in those engaged in occupations that require passage from warm or hot to cold air—e.g., miners and butchers.

Irritating gases and particulate matter in the atmosphere also contribute to the increased frequency of pneumonia in persons working in some industrial plants.

Lobar Pneumonia

Lobar pneumonia begins in one part of the lung and rapidly spreads until a barrier such as a lobar fissure is reached. In any one lobe all phases of the inflammation from the earliest to the latest are encountered, and it is therefore impossible to speak of "stages" in lobar pneumonia.

Pathogenesis. The causative bacteria, most frequently pneumococci, enter through the respiratory tract, and are trapped in a small mass of mucus. This plug of mucus is aspirated into a small bronchus and effectively blocks it. The pneumococci proliferate and spread into the distal alveoli. While still within the alveolar spaces, the bacteria incite an inflammatory reaction with hyperemia and with pouring into the alveoli of a fluid rich in protein and fibrinogen and containing a few red blood cells. Some bacteria enter the blood through the lymph and if more than can be destroyed in the liver and spleen escape, the result is the well known initial bacteremia of lobar pneumonia.

In three to six hours leukocytes are attracted to the region and migrate into the alveolar spaces. Soon thereafter, the fibrinogen is converted to fibrin. However, in the meantime the inflammatory edema has spread in a centrifugal manner. The progression of events is repeated in the next peripheral zone.

At the extreme periphery the lung is flabby and pink (because of the hyperemia and slight hemorrhage), and quantities of fluid exude from the cut surface. As the center is approached, the tissue becomes firmer (because of the clotted fibrin) and gray or yellowish gray (because of the abundant leukocytes); and the cut surface becomes dry (because of the squeezing of fluid from the fibrinous clot in the alveoli).

Death usually occurs at or near the height of the disease after an entire lobe has gone through the foregoing series of changes.

Pathologic Anatomy. The predominant pathologic picture is, therefore, that of gray hepatization. The lung or lobe is larger than normal, firm and gray. The pleura is covered

by a fine fibrinous exudate. The lung cuts with increased resistance, and the cut surface is gray, dry, and finely or coarsely granular. The interlobular septa are prominent and edematous. The alveoli are filled with a network of fibrin which connects with that in the adjacent alveoli through the pores of Cohn, and with many leukocytes and a few mononuclear cells and red blood cells. The alveolar walls are

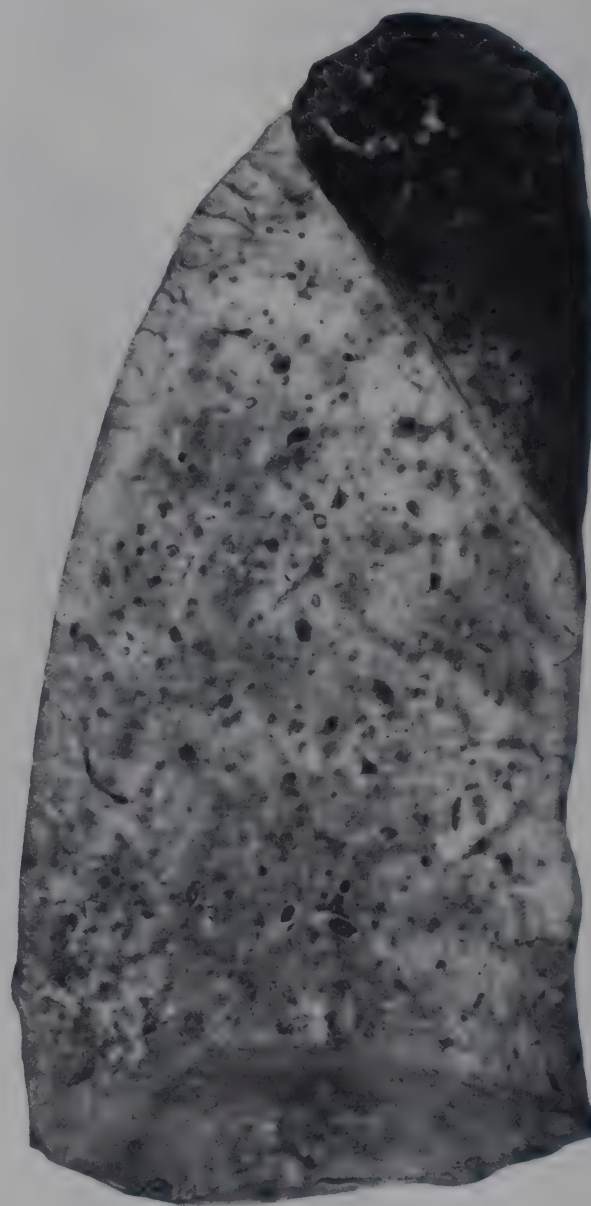


Fig. 121. Lobar pneumonia of lower lobe.

thickened by edema and by dilatation of the capillaries. The smaller bronchi may or may not contain a minimal amount of similar exudate. Grossly, the picture appears to be uniform throughout the entire lobe, but microscopic studies show beginning resolution where the process started.

Resolution is to be recognized by a decrease in firmness (because of the solution of the fibrin), and a transition from a grayish yellow to a grayish red or red color. The threads of fibrin contract, and the leukocytes phagocytize the bacteria. Mononuclear cells migrate into the region. Both leukocytes and mononuclear

cells undergo dissolution and liberate their intracellular enzymes. The enzymes digest the fibrin and other precipitated protein. Indigestible particles are phagocytized by mononuclear cells, and gradually all exudate is removed by expectoration or by absorption into the blood and lymph.

This description of the pathogenesis and pathologic anatomy of lobar pneumonia differs somewhat from that in the usual textbook, but it is based on convincing evidence of experimental pneumococcal lobar pneu-

fibrin organizes, and the pleura is thickened, or adhesions form. Of all patients with extensive fibrous pleural adhesions, 60 per cent give a history of pneumonia (Smith).

Organizing Pneumonia. Organization is to be recognized as a firm focus of gray fibrillar tissue with numerous small, yellow flecks. Microscopically, it is seen that the alveolar walls are intact, but that fibroblasts and capillaries have invaded the alveolar spaces along the threads of fibrin. Later, collagen is deposited. (Fig. 122; Fig. 63, p. 103).



Fig. 122. Organizing pneumonia; cut surface of lung as seen with a lens, showing scar tissue extending through the lung, and points of yellow opacity produced by fatty cells. (MacCallum.)

monia in dogs (Robertson), in monkeys (Loosli), and in rats (Wood), and careful studies of pneumococcal lobar pneumonia in man (Loeschcke).

Spread from one lobe to another is a repetition of the same succession of changes initiated by soiling of one or more bronchi of the secondarily involved lobe by fluid or exudate aspirated into it from the initially involved lobe.

About 50 per cent of lobar pneumonia is in the right lung, 40 per cent in the left, and 10 per cent in both. The ratio of involvement of the lower lobes to the upper lobes is 9:1.

Sequelae in the Lung. In the great majority of patients with lobar pneumonia the exudate resolves, and in a few weeks the pulmonary tissue is entirely normal. In the pleura, the

Complications. The frequency of all complications in lobar pneumonia is greater in the fatal cases since they all influence the outcome unfavorably. In a significant number, there is an excessive accumulation of fluid—pleurisy with effusion. The lung is compressed, and there may be considerable respiratory embarrassment. The most important complication is empyema—purulent inflammation of the pleura, which occurs in 5 per cent and carries a mortality of 25 per cent. The pleural cavity is filled with a thick yellow pus or a part of the cavity is walled off by adhesions, and locules are similarly filled. The lung is atelectatic, and the pleural surfaces are covered by a thick, yellow, fibrinous exudate.

Fibrinous pericarditis (Musser and Norris), otitis media and mastoiditis, acute vegetative

nia varies from year to year, and from place to place. Before the use of specific treatment, the average mortality was 35 per cent. The figures for the individual types were 30 per cent in Type I, 37 per cent in Type II, 46 per cent in Type III, and 23 per cent for the higher types. With serum a comparable figure for Type I is 16 per cent and for Type II, 22 per cent. The sulfonamides, penicillin, and aureomycin have further reduced the mortality to less than 5 per cent. The higher mortality of Type III is the result of limited phagocytosis of this type because of the thick capsule.

Bronchopneumonia

“Bronchopneumonia” is the term used to designate those nonsuppurative inflammatory conditions of the lung which are patchy, irregular, or lobular in distribution.

Pathologic Anatomy. The pleural cavity may contain a small amount of cloudy fluid, and the pleura is covered by a fine fibrinous exudate. There is rarely an excessive accumulation of fluid, and the purulent pleurisy of lobar pneumonia is not seen. In the fulminating types the fluid is occasionally hemorrhagic. On palpitation roughly spherical, irregular, poorly outlined foci of increased consistency are readily demonstrated, corresponding to the areas of radiopaqueness on the radiograph. These foci vary with the character of the exudate—grayish yellow for white cells, red for red cells, limpid for a fluid or cellular exudate, and firm for a fibrinous exudate. Occasionally, the foci are large and partially fused to form a more uniform consolidation—confluent bronchopneumonia. On pressure a droplet of pus can be expressed from each focus, and the smaller and larger bronchi are filled with a thick, viscid fluid. Rarely there is suppuration in some foci, and an abscess is the result. The mucous membrane of the bronchi and trachea is swollen and red. The unconsolidated lung is usually firm and dark red. The tracheobronchial lymph nodes are large and soft.

The character of the exudate varies from case to case, and from part to part. The bronchioles are filled with polymorphonuclear leukocytes and amorphous debris. The bronchiolar walls are edematous and infiltrated with lymphocytes and leukocytes. The alveolar walls are thickened and the capillaries di-

lated. The alveoli contain an exudate consisting of a variable mixture of fluid, leukocytes, red cells, and fibrin. In patients with a preceding disease such as measles or influenza, the alveoli are in part lined by a hyaline, homogenous, cell-free membrane, 10 to 50 microns thick. The interlobular septa are edematous, and the distended lymphatics are frequently occluded by fibrous thrombi. The lymph nodes show edema and hyperplasia.

Predisposing Factors. Bronchopneumonia is more frequently a secondary than a primary disease; consequently, it is seen as a terminal event in debilitation, cardiac failure, and cancer, and after aspiration of vomitus into the bronchi and after diseases producing slight to moderate inflammation of the respiratory tract, such as measles, whooping cough, scarlet fever, and influenza. These facts indicate that the normal defense of the lung against the bacteria that cause bronchopneumonia is high, but that with added damage the microorganisms can gain a foothold. Occlusion of the bronchus with retention of secretion is also an important contributing factor.

Bacterial Causes. *Primary Bronchopneumonia.* The varieties of bacteria found in primary bronchopneumonia vary with the city and year, but in general about 15 per cent are caused by the pneumococcus, 40 per cent by the streptococcus, 10 per cent by the staphylococcus, 4 per cent by the influenza bacillus, 3 per cent by Friedlander's bacillus, and 13 per cent by a mixture of bacteria. In 25 per cent no specific organism can be isolated (Cole). Of the pneumococci, Types III, VII, VIII, IX, XVIII, and XX are the more common. *Streptococcus viridans* is a rare cause (Solomon and Kalkstein).

Secondary Bronchopneumonia. The greatest care must be exercised in the evaluation of the presence of bacteria in the sputum in secondary bronchopneumonia. In one comparative study pneumococci were present in the sputum in 65 per cent of cases, but were recovered from the lung in only 30 per cent (Birge and Havens).

Interstitial Bronchopneumonia

In a not inconsiderable number of persons following an acute contagious disease such as measles, whooping cough, or influenza, a peculiar type of inflammation of the lung de-

velops, which has been termed by MacCallum "interstitial bronchopneumonia."

Pathologic Anatomy. The pleural cavity contains a large quantity of thin, turbid fluid in which there is a brown, granular sediment and a few shreds of fibrin. The pleura is covered by a thin layer of fibrin, and there are



Fig. 123. Interstitial bronchopneumonia.
(MacCallum.)

subpleural petechiae and ecchymoses. In cases in which the disease has persisted for some days, there is beginning organization of the fibrin on the pleural surface. The lungs are small, and there are small and large foci of atelectasis, partly the result of the pleural effusion and partly the result of obstruction of the bronchi.

On section of the lung numerous reddish yellow foci, from 4 to 8 mm. in diameter, are seen to project above the surface of the surrounding lung. In the center of each of these

foci, a bronchus can be identified, and from the lumen of the bronchus a thick yellow or hemorrhagic fluid can be expressed. The interlobular septa are prominent and frequently appear as gray, translucent, interlacing bands. The smaller bronchi are filled with pus, and the mucosa of the entire tracheobronchial tree is swollen, red and in many instances ulcerated. The tracheobronchial lymph nodes are slightly enlarged and soft. The pathologic changes are largely confined to the wall and the lumen of the smaller bronchi. In most instances the bronchial epithelium is desquam-

not show extensive involvement of the pulmonary parenchyma. The lymphatics in the walls of the bronchi and in the interlobular septa are dilated, and frequently filled with a delicate fibrinous thrombus. In persons who survive for several weeks there is evidence of organization of the exudate both within the bronchi and within the bronchial wall.

Incidence and Causes. This type of pneumonia is seen both in children and in adults, particularly in association with epidemics of influenza and the acute exanthemic diseases. A great variety of bacteria may be isolated

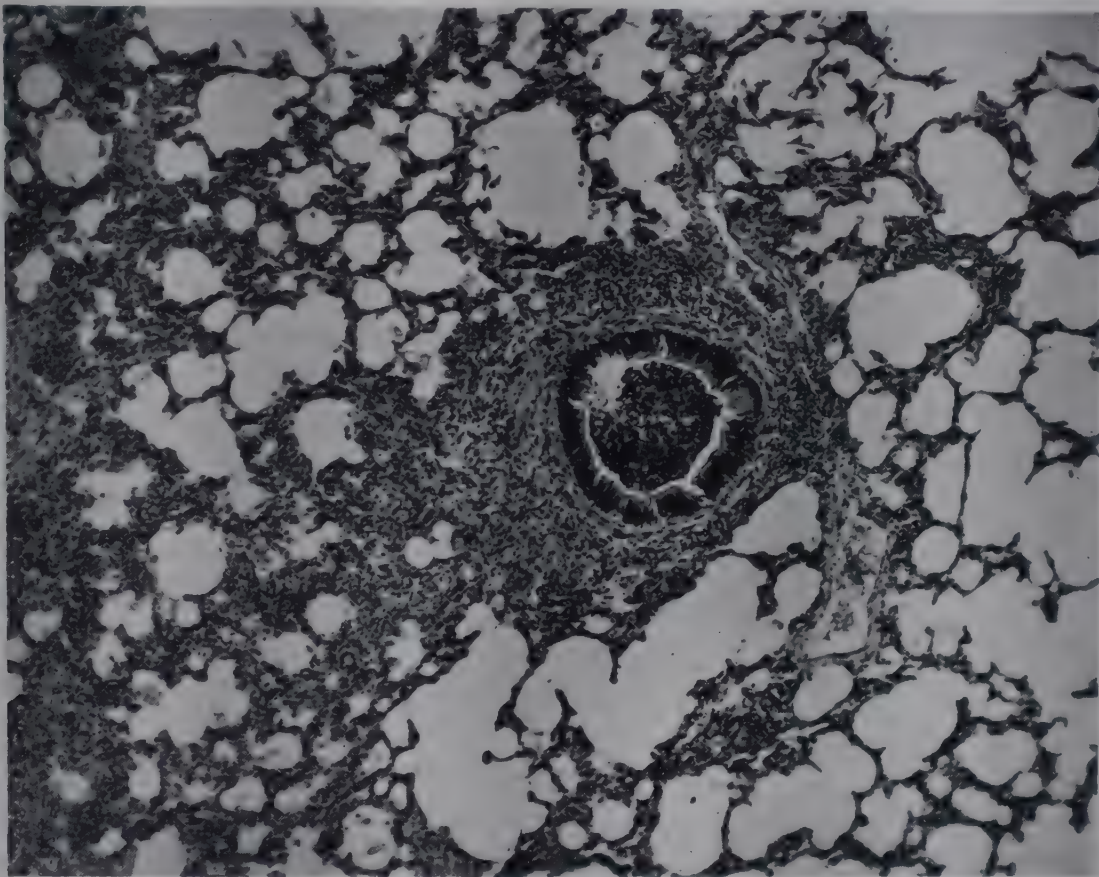


Fig. 124. Interstitial bronchopneumonia.

ated or ulcerated, and the lumen is filled with an exudate composed of mononuclear cells and leukocytes. The wall of the bronchus is greatly thickened as the result of edema, hyperemia, and cellular infiltration. The edema separates the individual elements of the normal bronchial wall; and the predominant cells are the mononuclear cell and the lymphocyte, with only an occasional polymorphonuclear leukocyte. This great increase in the thickness of the bronchial wall is responsible for the gross appearance, in that the nodules projecting on the surface represent the walls of individual bronchi and bronchioles. In a few of the surrounding alveoli there is an inflammatory reaction composed of large masses of dense fibrin, mononuclear cells, and a few leukocytes. However, the typical example does

from the respiratory tract. In most cases *Streptococcus haemolyticus* can be cultured, and bacterial stains of the tissues show large numbers of streptococci in the lumens of the bronchi and in the dilated lymphatics (Reichle and Moritz). There is some evidence that the *Streptococcus* is not the sole causal agent. McCordock and Muckenfuss have shown that pneumonia of a similar morphological pattern may be produced in rabbits by the simultaneous intratracheal injection of vaccinia virus and of bacteria.

Clinicopathologic Correlation. The excessive accumulation of fluid in the pleural cavity, with consequent atelectasis, and the obstruction of the smaller bronchioles with an exudate, combine to produce intense cyanosis and respiratory difficulty, manifested as dysp-

nea. The intensity of the inflammatory reaction throughout the entire tracheobronchial tree results in a fulminating course and a high degree of systemic reaction, such as headache, anorexia, and muscular pains.

Staphylococcal Pneumonia

Not infrequently in association with staphylococcal pyemia there are small or large abscesses throughout the lung, with a surrounding area of bronchopneumonia from which the *Staphylococcus* may be cultured. On the other hand a few cases of a definite pneumonic process without other evidences of pyemia must be recognized as primary staphylococcal pneumonia.

Pathologic Anatomy. Typically the pleural cavity contains a moderate amount of cloudy, yellow or hemorrhagic fluid. The pleural surfaces are covered by a fibrinous exudate. Many small, firm nodules, varying from 1 to 10 mm. in diameter, are discovered on palpation of the lungs. On cut section these nodules are seen to be composed of a centrum of thick, semifluid pus, and a peripheral zone of partially necrotic debris and hyperemic tissue. The intervening lung substance is hemorrhagic and in part consolidated. The bronchi are filled with thick pus, and the mucosa is swollen and hyperemic. The abscesses show the usual microscopic characteristics of this type of pathologic change. There is infiltration with many polymorphonuclear leukocytes and only a few mononuclear cells and lymphocytes (Wollenman and Finland).

Staphylococcal pneumonia is most common in children, but epidemics in adults have been reported (Chickering and Park; Finland, Peterson, and Strauss). The mortality rate is extremely high. There is great prostration and extreme cyanosis from the beginning, and death usually occurs on the sixth to the tenth day.

Abscess and Gangrene of the Lung

Abscesses of the lung may be large and single, or numerous and small throughout one or more lobes of the lung. Pathologic changes are essentially the same in both.

Pathologic Anatomy. There is a central focus filled with yellow, thick, fluid or semifluid material, surrounded by a zone of more dense yellow tissue. At the extreme periphery

in acute cases there is a red zone of hyperemia, and in the chronic cases a gray fibrillar zone of organization varying from 1 to 4 mm. in thickness. Microscopically, the usual structure of an abscess is observed, with a varying amount of tissue reaction, depending upon the age of the abscess. If the abscess has opened into a bronchus, the mucosa of this bronchus will be swollen, red, and velvety. The lumen is likely to contain a quantity of thick mucinous material. If the abscess of the lung comes in contact with the pleura, an acute fibrinous pleurisy over the area of the abscess will usually result. Perforation into the pleural cavity is associated with empyema or pyopneumothorax, and a broncho-pleural fistula is established.

The state of the surrounding lung is entirely dependent upon the pathogenesis of the abscess. In cases following pneumonia, there is likely to be both an acute and organizing pneumonia. In cases following the aspiration of a foreign body, or in the postoperative types, the remaining tissue of the lung may be essentially normal. A number of abscesses of the lung are associated with bronchiectasis (Maxwell).

Gangrene. In some cases the walls of the abscess are reddish green, and the tissue for a distance of 2 or 3 cm. is definitely necrotic. There is little reaction of the connective tissue in the neighborhood, and the contents have a putrid odor. The tissue about the cavity contains numerous fusiform bacilli and spirochetes. This type of lesion is usually designated "gangrene of the lung," but should be clearly distinguished from other types of gangrene which are caused by ischemia or by anaerobic bacilli (Kline).

Solitary Abscess. Solitary abscess of the lung may occur at any age and is definitely more common in the right lung than in the left. Solitary abscesses are frequently observed after operations on the upper respiratory tract and in association with bronchiectasis and carcinoma of the bronchus. A few cases are associated with foreign bodies in the bronchi, or occur as a complication of pneumonia. Multiple abscesses of the lung are clearly a part of systemic pyemia. In from 5 per cent to 10 per cent of all cases of abscess of the lung there is an associated abscess of the brain (Maxwell).

Pathogenesis. There are two possibilities:

(1) that the causal agent reaches the lung through the bronchial tree—bronchogenic; and (2) that the causal agent is brought to the lung by the blood stream—hematogenous (Cutler and Schlueter). Most observations in man and animals indicate that the hematogenous route is the usual one, although it cannot be denied that the bacteria are aspirated in a few cases, especially when there is gangrene. According to the work of Van Allen, a combination of bacteria in the bronchial tree and pulmonary embolism, with consequent decreased vitality of the tissues, may be an important causal factor.

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Tuberculosis: General Considerations

Any basic understanding of the pathology and epidemicity of tuberculosis must begin with an examination of the mortality curve of the disease. The figures for the registration area of the United States are shown in Fig. 125. It is seen that there are two peaks of mortality: one in the first few years of life and another

acteristic lesion known as the "tubercle." The tubercle consists basically of three parts, a central giant cell, a midzone of epithelioid cells, and a peripheral zone of general nonspecific reaction. The central giant cell varies from 100 to 500 microns in diameter, and sends prolongation of its cytoplasm into the midzone

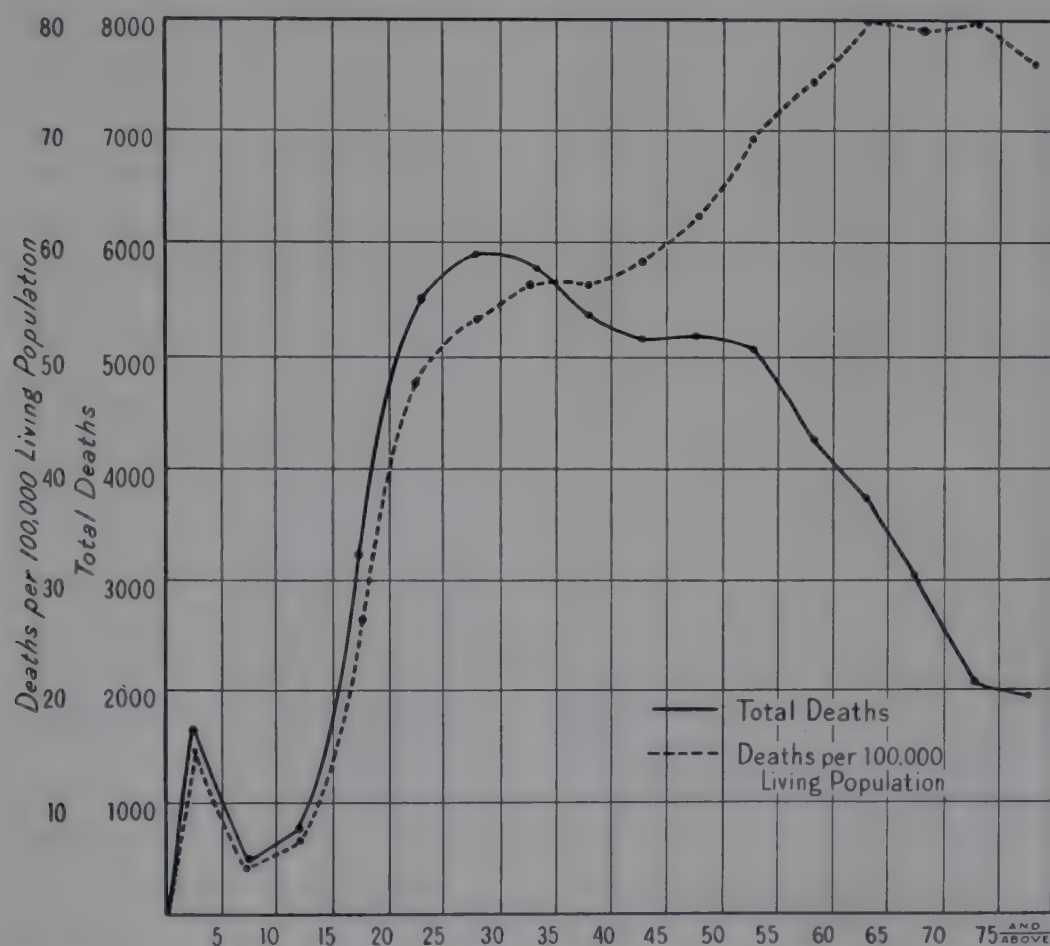


Fig. 125. Deaths from all forms of tuberculosis in the Registration Area of the United States.

in the third and fourth decades. The lesions in the two are quite different, and are designated as the "first infection" and the "reinfection," respectively.

Reaction to the Tubercle Bacillus

When living or dead tubercle bacilli are introduced into the tissues of an animal organism, there results a typical and highly char-

acteristic lesion known as the "tubercle." The tubercle consists basically of three parts, a central giant cell, a midzone of epithelioid cells, and a peripheral zone of general nonspecific reaction. The central giant cell varies from 100 to 500 microns in diameter, and sends prolongation of its cytoplasm into the midzone

homogenous or very finely vacuolated. The nuclei are lightly chromatic and relatively large. With stains for reticulum, a fine network may be demonstrated between the cells. The peripheral zone consists of a band 50 to 100 microns in thickness in which there is proliferation of fibroblasts and infiltration with lymphocytes, mononuclear cells, and plasma cells. Inside of this peripheral layer there are no blood vessels, and therein the tubercle differs from all other granulomas—that the actual lesion is avascular.

The histogenesis of this fully developed lesion may be studied serially in experimental animals. The initial reaction for from six to twenty-four hours is an exudation of fluid and polymorphonuclear leukocytes. At the end of this time the leukocytes begin to undergo necrosis, and there is a migration of monocytes into the area. These monocytes ingest both the tubercle bacilli and the dead leukocytes. The tubercle bacilli are broken down in part, and the characteristic phosphatide is liberated within the cells. Under the influence of this chemical substance the monocyte changes into an epithelioid cell, and some of the latter fuse to form the central giant cell. After some days or weeks there is proliferation of the surrounding fibrous tissue and infiltration with lymphocytes.

Transmission

There are two principal portals of entry of the organism, the respiratory tract and the gastro-intestinal tract. In those cases in which the organism enters the respiratory tract and produces a lesion in the lung, droplet infection from close contact with those with tuberculosis and dust in the atmosphere are the important means of transmission. The tubercle bacillus lives for many days or months in the dry state. In infections through the gastro-intestinal tract, milk from tuberculous cows is the most important source. In a few instances the bacilli so ingested invade the body through the tonsil or the pharyngeal mucosa and bring about massive caseation of the cervical lymph nodes. Within the stomach the high acidity prevents invasion of the wall, and in many instances destroys the organisms. If they escape into the lumen of the intestine, the primary lesion is found in the small lymph follicles of the mucosa of the ileum, with case-

ation of the draining lymph nodes in the mesentery. In addition to these two common portals of entry there are the rarer instances in which the disease is acquired by direct contact and the initial lesion is on the surface of the body (see Chapter XXVII, p. 250).

Causal Agent

Identification and Isolation. In general, there are three procedures available to the pathologist or clinician to demonstrate the causal agent in tuberculosis—staining, culture, and animal inoculation. In the body fluids and excreta and in tissues the characteristic acid-fastness of the tubercle bacillus is readily demonstrated with special stains. Acid-fast bacilli found in the excreta from the region of the perineum must be distinguished from another acid-fast organism, known as *Mycobacterium smegmatis*, by special staining methods, or by inoculation into animals, as the latter organism is nonpathogenic. Growth of the tubercle bacillus on artificial culture media requires considerable care and precision (Corper and Cohn). In general, the organism requires the presence of glycerin, and when workers deal with pathologic material some growth-inhibiting substance must be added to prevent overgrowth with the common bacteria found in sputum and other fluids. The most satisfactory method for the demonstration of both the presence and the pathogenicity of a given acid-fast bacillus is inoculation into guinea pigs.

Relation of Types of the Organism to Human Disease. The source of the infective material and the portal of entry into the body will in large part determine whether a given example of human tuberculosis is caused by the human or the bovine strain. In general, tuberculosis of the cervical lymph nodes at all ages, tuberculosis of the intestine and mesenteric lymph nodes, and tuberculosis of the bones and joints in children are caused by the bovine bacillus.

Relation of Tissue Reaction to Chemical Constituents. With the isolated and partially purified constituents of the tubercle bacillus it has been possible to study the reaction of the tissues to each component, and thus synthesize the reaction to the bacillus as a whole.

Protein. Injections of the protein fraction into a normal animal give rise to an increase

leukocytes, a decrease of lymphocytes and monocytes, an increase of temperature, and an accumulation of plasma cells, with slight hemorrhage at the local site of injection (Sabin, Miller, Doan, and Wiseman; Miller, Sabin, Doan, and Forkner). As small an amount as 1 mg. in a tuberculous guinea pig may produce death in from six to twenty-four hours. Finally the skin reaction known as the "tuberculin test" depends solely on the protein fraction of the bacillus.

Carbohydrate. The polysaccharide provokes the same change in the circulating white blood cells as the protein does, and to a certain extent will call forth a general toxic reaction and death in tuberculous animals. Locally it is positively chemotactic and toxic to polymorphonuclear leukocytes.

Lipids. Each of the three general constituents of the lipid fraction, a phosphatide, an acetone-soluble fat, and a wax, gives a distinctive and characteristic reaction in the tissues. Injection of a suspension of the phosphatide in water into the peritoneal cavity of a rabbit is followed within a few hours by active phagocytosis of the lipid by monocytes derived from the milk spots of the omentum. For a period of three to four days the engorged lipid appears as large vacuoles, but gradually the material is broken into finer and finer vacuoles so that the cytoplasm becomes foamy on the fifth to the seventh day. At the beginning of the third week epithelioid cells with two nuclei are seen, and rapidly thereafter the typical Langhans giant cell forms. At this same time lymphocytes in considerable numbers collect about the focal lesions, and the center of many of them undergo caseation. The specific fatty acid, phthioic acid, derived from all of the three lipid fractions, gives a reaction in tissue similar to that of the phosphatide except that the earlier stages are lacking. This indicates that the phosphatide is reduced in the cells to some state comparable to the fatty acid. The acetone-soluble fat produces a most complex reaction. The diffuse epithelioid reaction is probably due to the contained phthioic acid. In addition there is a general infiltration of the tissue with leukocytes, a great increase of fibroblasts, lymphocytes, and plasma cells, and an increase of small blood vessels with fragile walls and consequent hemorrhage. The unsaponifiable waxes, probably complex phos-

phatides, are acid-fast and thus responsible for this property of the organism. An unsaponifiable higher alcohol derived from the waxes produces a remarkable proliferation of fibroblasts, both diffusely and in small clumps (Sabin).

Effect of Antibiotics. The use of chemotherapeutic agents gives promise of favorably influencing the course of tuberculous infections. In guinea pigs streptomycin prevents spread of the bacilli and the lesions present are small and fibrotic (Feldman, Hinshaw, and Mann). In man, there is significant fibrosis of existing lesions (Baggenstoss, Feldman, and Hinshaw).

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XXVI

Pulmonary Tuberculosis

The lesions of active tuberculosis in the lungs may take on one of two characters designated as first infection and reinfection types. In addition two other anatomic changes are generally considered as tuberculous—calcified nodules and apical fibrous scars. Each of these will be discussed separately.

Clinically Manifest First Infection Pulmonary Tuberculosis

In the child or the adult who has died of airborne first infection tuberculosis there is an almost constant pathologic picture, with distinctive lesions in the lungs, tracheobronchial lymph nodes, viscera, and brain.

Primary Lesion in the Lung. *Pathologic Anatomy.* In any part of the lung, but usually just beneath the pleura, there is an irregularly spherical or pyramidal, yellow, friable, firm nodule, varying from 5 to 20 mm. in the greatest dimension. The architecture of the lung is entirely destroyed; the margin is irregular but sharp; and the surrounding tissue is slightly firmer and redder than the tissue at a distance. Microscopic study reveals complete caseation of the great part of the nodule, but examination of sections stained for elastic tissue shows a framework of alveolar walls. At the edge of the caseous mass there is inflammatory tissue, consisting of young fibrous tissue, lymphocytes, and tubercles (Pagel and Price).

Clinicopathologic Correlation. The primary nodule represents an increase in consistency and replacement of the air. It is therefore visible on the radiograph as an area of radiopaqueness, and may be demonstrable by percussion and auscultation. Since it does not communicate with a bronchus, the sputum does not typically contain bacilli.

Lesions in the Tracheobronchial Lymph Nodes. *Pathologic Anatomy.* The tracheo-

bronchial lymph nodes are greatly enlarged and completely caseous. Only a small rim of living tissue in the capsule is observable, and in this there is lymphocytic infiltration and tubercle formation.

Clinicopathologic Correlation. The involved nodes are in the midline, and enlargement of

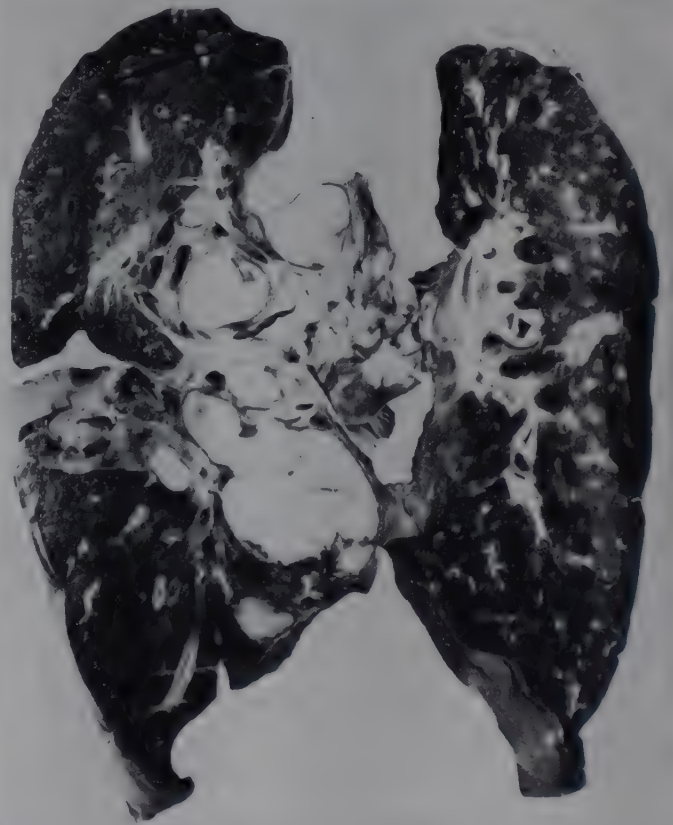


Fig. 126. First infection tuberculosis of the lungs. Note small caseous lesion in lower lobe and massive caseation of lymph nodes. (Photograph by courtesy of Dr. Oscar Auerbach.)

them causes a widening of the mediastinal shadow as determined by radiography and by percussion. The nodes at times press on the bronchi and cause stenosis.

Lesions in the Viscera. *Pathologic Anatomy.* Throughout the lungs, liver, spleen, and kidneys, and to a less extent in other organs, small, gray, translucent, firm nodules, 1 to 2 mm. in diameter, are abundant—miliary tubercles. The source of the vascular dissemina-

tion is usually found in the lung. A large, caseous mass, either a pulmonary lesion or a lymph node, projects into or has eroded into a branch of the pulmonary veins (Auerbach).

Clinicopathologic Correlation. The miliary foci are easily demonstrated in a radiograph of the chest and can be seen in the choroid by ophthalmoscopic examination. The disease in the liver, spleen, and kidneys may cause these organs to become palpable.

Lesions in the Brain. In the vast majority of patients with first infection tuberculosis, the immediate cause of death and the most important signs and symptoms are attributable

chronic tuberculosis is most often in the upper lobe of the lung. The essential nature of the lesion is fibrosis on the one hand and destruction of tissue and cavitation on the other hand. The pleural cavity over the upper lobe or over the entire lung is completely obliterated by dense fibrous adhesions, and the pleura is thickened. The upper part of the lung is dense, firm, and contracted, but one or more cavities may be palpated. The cavities are roughly spherical spaces, lined by a type of tissue which varies from a shaggy, grayish yellow, friable membrane, with numerous tubercles in the adjacent tissue, to a smooth, gray, firm



Fig. 127. Caseous mass projecting into pulmonary vein. Miliary tuberculosis. (MacCallum.)

to tuberculosis meningitis (full discussion, p. 256).

Clinically Manifest Reinfection Pulmonary Tuberculosis

The second peak of deaths from tuberculosis begins at puberty, increases to the middle of the third decade, and then gradually declines. There are prominent changes in the lungs and less conspicuous lesions in the other organs.

Chronic Pulmonary Tuberculosis. *Pathologic Anatomy.* In the typical example of reinfection pulmonary tuberculosis there are three distinctive pathologic changes: (1) the apical lesion, (2) bronchogenic tuberculosis, and (3) tuberculous pneumonia.

THE APICAL LESION. The principal lesion of

wall, with few or no tubercles. In all types of cavities there are free or engaged columns which cross from one side to the other. Cross-section reveals that these are large blood vessels occluded by a thrombus or a bronchus. In the patient who has died after a severe hemorrhage, one of the vessels will be found to contain fluid blood, and a small perforation in the wall or in a small aneurysm can usually be demonstrated.

In the lung about the cavities there are extensive fibrosis and contraction. Most of the alveoli are obliterated, and the remaining spaces are irregularly deformed and lined with cuboidal cells. Dispersed throughout the fibrous tissue are numerous tubercles, some completely caseous and others with epithelioid cells and giant cells.

In the bronchi leading from the cavities

there is frequently an ulcerative tuberculous process (Reichle and Frost). The lymph nodes, in striking contrast with those in the first infection type, are not greatly enlarged, and at the most show only a few tubercles, with minimal caseation. In almost every case the calcified nodules of a first infection tuberculosis can be identified (Opie).

BRONCHOGENIC TUBERCULOSIS. From time to time small numbers of bacilli discharged into the bronchi from a cavity may be aspirated into other parts of the lung. Here they

combination of changes appears as a uniform, bluish gray, translucent consolidation, hence the name, "gelatinous pneumonia." With further progress the exudate and tissue undergo caseation and the focus appears as a firm, yellow, finely granular, friable mass—caseous pneumonia. In the usual type there are isolated foci, but occasionally an entire lobe is involved.

TUBERCULOUS PLEURISY. In minimal lesions there may be an associated pleurisy with accumulation of a clear fluid (Gordon, Charr,



Fig. 128. Clinically manifest reinfection tuberculosis of the lungs: cavitation and fibrosis of both upper lobes, and bronchogenic tubercles of both lower lobes. (Photograph by courtesy of Dr. Oscar Auerbach.)

form a characteristic lesion known as "bronchogenic tuberculosis." Scattered throughout the lung, more abundant in proximity to the cavity, are clusters of yellow, caseous tubercles. In the center of each on the cut surface a small depression is seen. There is a central caseous mass, representing the former lumen and inner wall of the bronchus, with surrounding inflammation. In the adjacent tissue there is caseous pneumonia, tubercle formation, or fibrosis, depending on the severity and age of the process.

TUBERCULOUS PNEUMONIA. If large numbers of bacilli are aspirated into the lung, a different reaction ensues. The alveoli are filled with a protein-rich, viscid fluid, and a few mononuclear cells. The alveolar walls are edematous and hyperemic. Grossly this com-

and Savacool). In advanced pulmonary tuberculosis the pleura is thickened and the pleural cavity obliterated by fibrous adhesions. Occasionally there is a suppurative pleurisy—tuberculous empyema (Ehler).

THE HEART IN PULMONARY TUBERCULOSIS. The extensive fibrosis of the lung in some types of pulmonary tuberculosis may obliterate a sufficient amount of the vascular bed to result in hypertension in the pulmonary circuit and hypertrophy of the right side of the heart—cor pulmonale. This lesion is encountered in about 5 per cent of all deaths from pulmonary tuberculosis (Ackerman and Kasuga).

Lesions in Other Organs. In a significant number of patients with chronic pulmonary tuberculosis there are in addition ulcerative

tuberculosis of the larynx (see p. 251) and ulcerative tuberculosis of the intestine (see p. 251). Less commonly there are tuberculous lesions in the other organs (see the following chapter, p. 250). In contrast with the frequency of miliary tuberculosis in the first infection, widespread vascular dissemination in reinfection tuberculosis is unusual.

Acid-Fast Bacilli in Nontuberculous Pulmonary Disease. In a rare patient acid-fast bacilli, not pathogenic for guinea pigs, are present in the sputum but with pulmonary changes of abscess or bronchiectasis. These are saprophytic acid-fast bacilli (Cory).

Healed and Latent Tuberculosis

In addition to the signs of clinically manifest tuberculosis in the lungs, two pulmonary

different times show considerable variability in the incidence of pulmonary nodules at different ages. The studies of Opie and of Carnes, given in Table 12, are probably representative for urban centers of the United States. The lower incidence in the Baltimore series between ages 2 and 18 may be an index of decreasing incidence of tuberculosis in 1938 as compared to 1916.

Causal Agent. On the basis of the early anatomic studies in Europe and correlation with the results of tuberculin tests, it was assumed that the sole cause of calcified pulmonary nodules was the tubercle bacillus; that is, they were believed to be healed or latent first infection tuberculosis.

More recent studies cast doubt on this conclusion, at least for certain geographic regions of the United States. Cox and Smith identi-

TABLE 12. INCIDENCE OF CALCIFIED NODULES IN THE LUNGS IN RELATION TO AGE IN PERCENTAGES

Age in Years	St. Louis 1916 (Opie)	Baltimore 1938-40 (Carnes)
Under 1	0	2.0
1- 2	0	4.8
2- 5	27.3	4.8
5-10	33.3	18.2
10-18	62.5	39.2
18-30	100.0	83.3
30-50	100.0	86.0
50-70	100.0	96.5
Above 70	100.0	100.0

lesions are observed frequently at autopsy, which have been considered by many as tuberculous in origin—fibrous or calcified nodules and apical fibrous scars. Inasmuch as each presents a different problem in evaluation, they will be discussed separately.

FIBROUS AND CALCIFIED NODULES IN THE LUNG AND TRACHEOBRONCHIAL LYMPH NODES

Pathologic Anatomy. Nodules showing a variable mixture of caseous, fibrous, and calcified elements are observed in all lobes of the lung, usually just beneath the pleura. Similar nodules occur in the tracheobronchial nodes, usually in the drainage area of the lesion in the lung. Microscopic study reveals little significant information. In some nodules there is ossification (Sweeny). In a minority there are multiple nodules in the lung and rarely widespread miliary foci of calcification.

Incidence. Reports from different cities at

fied *Coccidioides* in some calcified nodules and demonstrated that this organism may produce exactly the same combination of calcified nodules in lung and lymph node.

Probably more significantly it has been observed that recovery from pulmonary histoplasmosis is associated with the development of multiple calcified nodules in the lungs (Bunnell and Furcolow). Further many individuals with calcified nodules have a negative tuberculin reaction and a positive histoplasmin reaction (Palmer).

The only possible conclusion today is that some calcified nodules are related to coccidioidomycosis, others to histoplasmosis, and still others to tuberculosis. What the percentage of each is cannot be stated.

FIBROUS APICAL SCARS

The characteristic lesion is just caudal and posterior to the extreme apex. An irregular

area of the visceral pleura is adherent to the parietal layer or is thickened, opaque, depressed, and firm. Thin and broad trabeculae of dense connective tissue extend into the lung. The bronchi are ectatic, and there is focal emphysema (Bunting). Microscopic examination reveals dense connective tissue and slight diffuse and focal infiltration with lymphocytes. Only rarely can tubercles be identified. Injection of these scars into guinea pigs causes tuberculosis in 75 per cent, establishing the tuberculous nature of the condition. Fibrous thickening of the pleura without fibrosis of the lung, on the other hand, does not contain tubercle bacilli and should not be considered a specific lesion (Opie and Aronson).

Incidence. The incidence of apical scars has been reported from various communities from a few per cent to 30 per cent. In St. Louis in 1941 a study of 100 lungs of white persons showed an apical scar in 33 per cent. In the same group there were 93 with calcified nodules in the lungs and lymph nodes and 40 with calcified nodules in the spleen or liver. The two apices are involved with equal frequency.

Significance. Since at least 75 per cent of apical scars contain virulent tubercle bacilli, it must be logically assumed that the lesion has clinical significance. McPhedran and Opie followed a group of 96 persons who were less than forty years of age and who had latent apical lesions of four types. The per cent that developed clinically manifest tuberculosis within a period of a few years is shown in Table 13 (p. 246). In persons over forty, only 2 out of 34, or about 6 per cent, developed manifest disease.

Relation of First Infection to Reinfection Tuberculosis

It has been shown (1) that almost all persons with reinfection tuberculosis have lesions of a latent first infection, and (2) that the pathologic changes of the first infection and of the reinfection are as different as though they were two separate diseases. The correct evaluation of the significance of the two facts will determine our ideas of the pathogenesis, transmission, and control of tuberculosis.

Influence of the First Infection on Reinfection. Koch noted that an animal which had previously been infected with tubercle bacilli would react differently to a subsequent injection

of either the bacilli or their products—the Koch phenomenon. It is probable that the first infection and the reinfection represent an expression of the Koch phenomenon. The relative localization of bacilli at the initial lesion, the massive destruction of tissue, and the fibrosis of the reinfection fit in well with the known effects of the allergic state on inflammation, and represent the effect of hypersensitivity and immunity conferred by the first infection (full discussion, p. 109).

Another factor in evaluating the action of the tubercle bacilli in tissue is dosage. In the

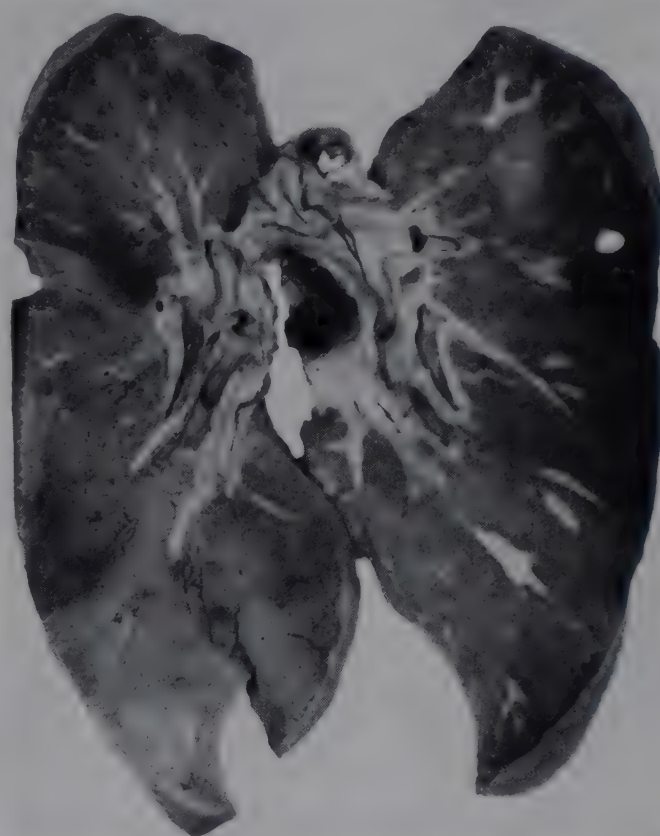


Fig. 129. Calcified nodules in the right upper lobe and in a tracheobronchial lymph node. (Photograph by courtesy of Dr. Oscar Auerbach.)

hypersensitive organisms an overwhelming dose produces massive necrosis (caseous pneumonia), a moderate dose multiple caseous tubercles (bronchogenic tuberculosis), while a minute dose may be handled and killed without extensive tissue change.

Vaccination in Tuberculosis. Humoral Antibodies. If this conclusion is correct, then it should be possible to vaccinate against tuberculosis. Calmette at the Pasteur Institute in Paris isolated a human tubercle bacillus and grew it for 230 successive generations during the course of thirteen years on a medium of 5 per cent glycerin-potato saturated with ox bile. At the end of this time the organism was still acid-fast, but had no virulence

for any laboratory animal. It is known as BCG (Bacille Calmette-Guérin). It may be given by injection or by mouth, and in general the reports indicate that a considerable degree of immunity to tuberculosis follows its administration. Opie and Freund find that tubercle

Bacteriologic Evidence. If the bacilli of the first infection persist in the nodules and subsequently enter other tissues to incite the re-infection, it should be possible to demonstrate them in the nodules, which it is not (Feldman and Helmholtz). Similarly, if the bacilli are

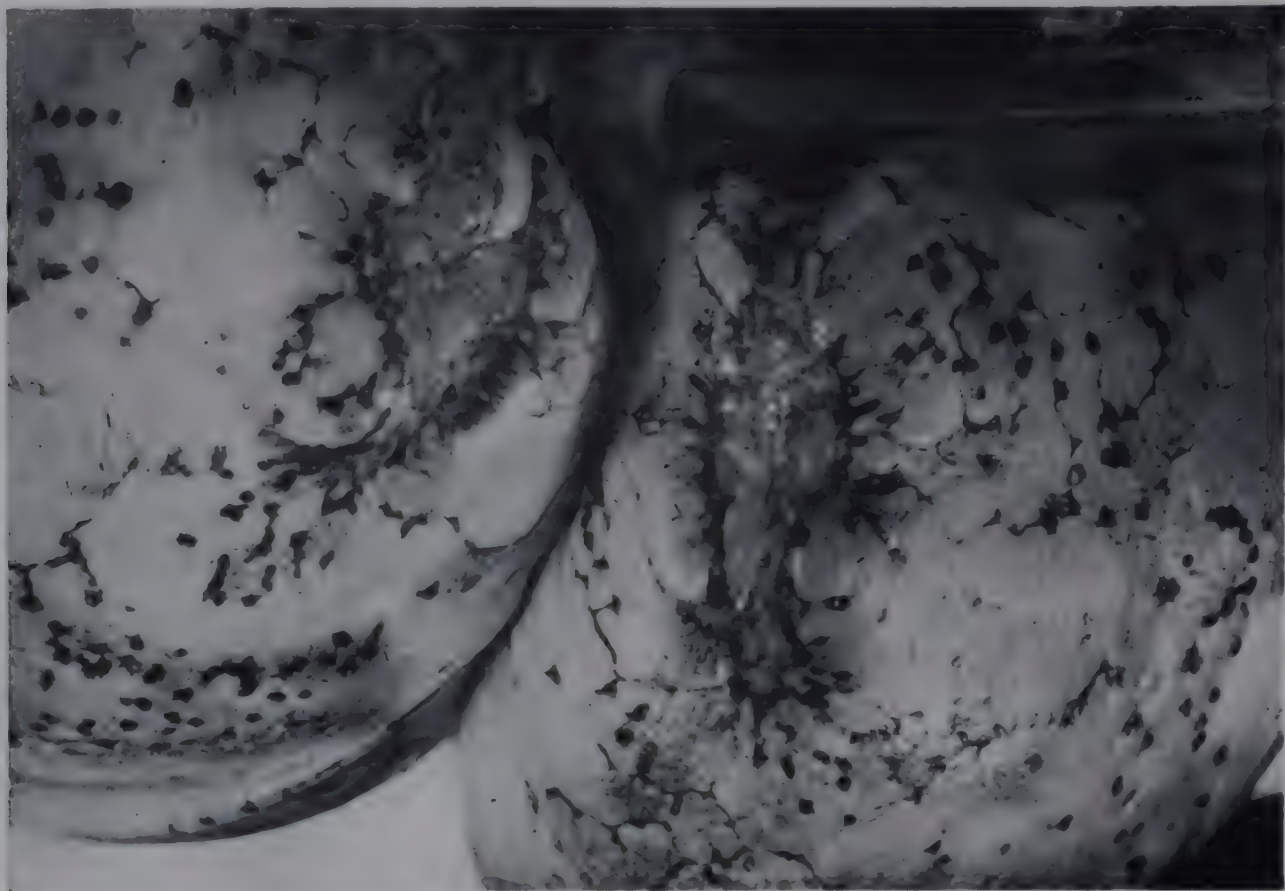


Fig. 130. Bilateral apical scars of latent reinfection pulmonary tuberculosis.

bacilli killed by heat serve as a vaccine almost as satisfactory as the living BCG, and studies in Jamaica indicate that this vaccine confers tuberculin positivity and an increased resistance to the disease (Wells, Flahiff, and Smith).

disseminated to the apex of the lung during the active phase, infectious lesions of some sort should be demonstrated, and they are not. *Anatomic Evidence.* Careful study of the latent calcified nodules and the latent apical lesions fails to reveal any continuity between

TABLE 13. FATE OF PERSONS WITH FIBROUS APICAL SCARS

Group	Extent of Lesion	Per Cent That Developed Manifest Tuberculosis
1	Scant	5.7
2	Half or more of apex above clavicle	25.0
3	Equivalent to minimal tuberculosis	47.8
4	Equivalent to moderately advanced tuberculosis ...	50.0

Endogenous versus Exogenous Reinfection. Logically there are two possible sources of the bacilli that cause reinfection tuberculosis: persistence from the first infection (endogenous) and introduction of new organisms from without (exogenous). Evidence as to which of these is the usual source may be marshaled along three lines, bacteriologic, anatomic, and epidemiologic.

the two, as is usually the case in related tuberculous lesions (Opie). Further, histologic study of the earliest apical lesion shows an essentially aerogenous infection with the initial reaction in the smaller respiratory bronchioles. *Epidemiologic Evidence.* If reinfection is exogenous, it is reasonable to believe that latent and manifest apical lesions would be present more frequently in those exposed to

tuberculous patients with positive sputa than in the general population. The groups studied most extensively are families in which one member has chronic pulmonary tuberculosis (Opie, McPhedran, and Putnam; Hahn), marital partners (Opie and McPhedran), at-

ates on the spread of tuberculosis in families. Figure 131 is introduced to give some idea of the method of study of a disease in families. Each vertical block represents one year of life, and the heavy lines with names are the life lines. The study began at the heavy line seven

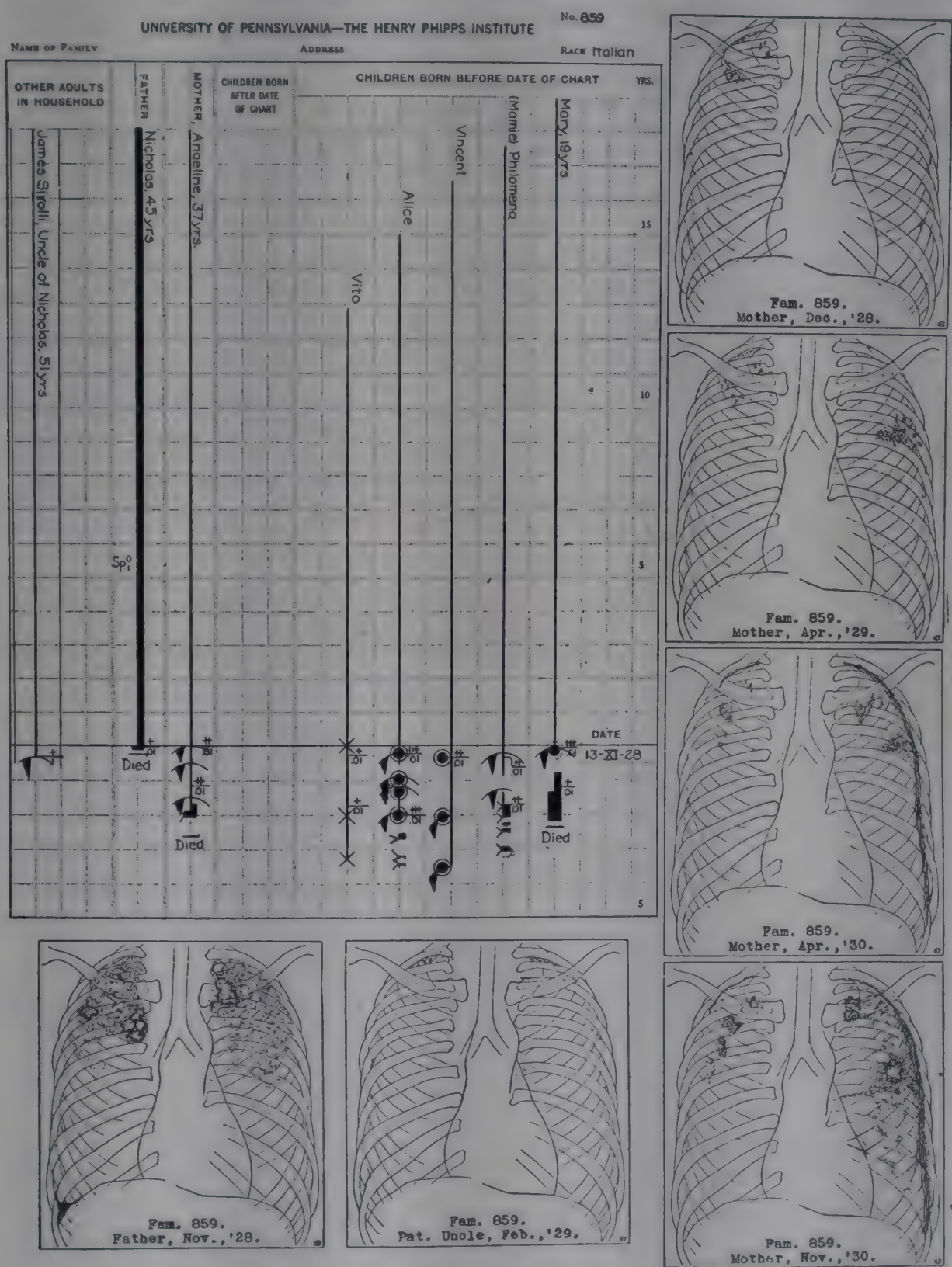


Fig. 131. Diagrams to illustrate a method for the charting of disease in a family. See text for explanation. (McPhedran and Opie: Am. J. Hyg., Vol. 22.)

tendants in sanatoria for tuberculosis, and medical students (Hahn, Muschenheim, and Freund). In every instance with radiographic study the incidence of apical lesion is higher than in comparable nonexposed groups. The most convincing data come from the studies by Opie, McPhedran, and their associ-

blocks from the bottom. The father and three children had clinically manifest disease, and the mother and five other children had a positive tuberculin reaction or latent lesion or both. Similar studies of families free of tuberculosis show a quite different picture. There is the usual incidence of first infection, but

far less latent or manifest reinfection (Opie and McPhedran; Beeuwkes, Hahn, and Putnam).

Racial Resistance. Closely related is the problem of racial resistance and susceptibility (Long; Lurie; Kallmann and Reisner; Dublin). It is well known that among primitive tribes first brought in contact with tuberculosis the morbidity and mortality are extreme. Among the Negroes of the United States a higher percentage brought into household contact with tuberculosis develop the disease than do white persons. The explanation of this may be found in dosage and in social and economic factors as well as in a postulated racial susceptibility. The explanation of the resistance of some animal species may be found in the presence of enzymes which rapidly hydrolyze the lipids (Gerstt, Tennant, and Pelzman).

Experimental studies in rabbits indicate there are two factors in racial resistance to tuberculosis: resistance against attack by airborne bacilli, and resistance to the ensuing disease (Lurie).

Summary. Most of the evidence cited in the preceding paragraphs favors the concept that the first infection influences the reinfection and that most reinfections are exogenous in origin. There are some facts and studies which cast doubt on both of these conclusions. The most convincing is the rarity of clinically manifest first infection lesions in the age group 12 to 30 years, despite the known and apparently decreasing incidence of calcified nodules and tuberculin positivity in these individuals. The problem is discussed in detail by Rich in his excellent book.

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XXVII

Extrapulmonary Tuberculosis

Tuberculosis of organs other than the lungs may be of two types: (1) primary in the sense that it is the first lesion of tuberculosis in any part of the body, and (2) secondary in the sense that there is a primary lesion of tuberculosis in some other organ or tissue.

Primary Sites of Extrapulmonary Tuberculosis

In most instances tuberculosis is either an airborne infection, or transmitted by milk from tuberculous cows. In rare instances, the primary lesions are acquired by direct inoculation or by placental transmission.

Congenital Tuberculosis. In tuberculous pregnant women, tubercle bacilli may lodge in the uterine sinusoids and cause lesions in the placenta (Schaefer). Tuberculosis of the fetus sometimes but not always results (Reichle and Wheelock).

Primary Tuberculosis of the Skin. The initial lesion appears in an inconsequential wound, where small, wartlike papules form small single or multiple verrucous patches—tuberculosis verrucosa cutis. The verrucae may persist for months or years. Soon after appearance of the dermal lesion, an indolent type of lymphangitis, as well as enlargement of the regional nodes, occurs (Scott).

Primary Tuberculosis of the Gastro-intestinal Tract. About 10 per cent of all tuberculosis in all parts of the world is caused by the bovine strain of the bacillus (De Gara). The bovine or human bacilli which enter the body for the first time through the alimentary tract invade the mucosa in the region of either the pharynx or the ileum.

Primary Tuberculosis of the Upper Intestinal Tract. In those countries (Scotland, England, and Denmark) where bovine tuberculosis is widely prevalent, about 50 per

cent of all tuberculosis of the cervical nodes is caused by the bovine bacillus.

TUBERCULOSIS OF THE TONSILS. From 0.25 to 6 per cent of all tonsils show evidence of tuberculosis, varying with the incidence of tuberculosis in the community. In those with pulmonary tuberculosis and a positive sputum, the incidence is as high as 75 per cent. Epithelioid tubercles form in the lymphoid tissue about the crypts. Bacilli are rarely demonstrable. In the primary infections, the disease is usually unilateral (Long, Seibert, and Gonzalez; Rather).

TUBERCULOSIS OF THE CERVICAL LYMPH NODES (SCROFULA, THE KING'S EVIL). The superior deep cervical nodes are most frequently affected. Further extension is by either the internal or the external jugular chain of nodes. The lymph nodes are greatly enlarged and converted almost entirely into caseous material. With progress of the disease, the nodes become adherent to one another, to the surrounding tissues, and to the skin, and often ulcerate through multiple sinuses onto the skin. In healing, there is extensive scarring and retraction of the skin (Thompson). Scrofula is a disease of the first fifteen years of life, and through improvement of general sanitation has decreased in frequency in the last fifty years.

Primary Tuberculosis of the Lower Intestinal Tract. The initial lesion is a small tubercle in the lymphoid tissue of the terminal ileum. The mesenteric lymph nodes are greatly enlarged and almost completely caseous (Reichle). With healing, there is calcification of the lymph nodes. The lesion in the intestinal wall usually ulcerates and is lost (Ferris).

The source of primary intestinal infection is infected milk. In the United States, the incidence of calcified nodules in the mesen-

teric lymph nodes of adults is not over 5 per cent.

Secondary Extrapulmonary Tuberculosis

In the succeeding sections, secondary tuberculosis of each organ system will be considered and the pathogenesis discussed.

TUBERCULOSIS OF THE SKIN

Aside from the inoculation type of tuberculosis of the skin, there are many clinical varieties of hematogenous tuberculosis and of tuberculosis caused by extension from underlying organs. The most common is lupus vulgaris.

Lupus Vulgaris. Discrete or conglomerate, proliferative or caseous tubercles in the dermis appear as small reddish brown spots or nodules. With progressive enlargement, the dermis is thinned and eroded. The ulcers are irregular and sharply outlined, and have a ragged, granular base. Lupus is seen chiefly on the nose, cheeks, forehead, ears, lips, and skin of the upper extremities (McCarthy).

Scrofuloderma. There is at first a firm nodule in the dermis which rapidly enlarges and caseates. Resolution takes place by liquefaction and absorption, or by ulceration and discharge of the contents.

Tuberculids. These are small, eruptive lesions which early show necrosis of the dermis, later involvement of the epidermis, and finally ulceration.

TUBERCULOSIS OF THE RESPIRATORY PASSAGES

About 10 to 30 per cent of those with active pulmonary tuberculosis have associated tuberculosis of the respiratory passages, most commonly in the bronchi, next most commonly in the larynx, and least commonly in the trachea (Huang).

Pathologic Anatomy. The structures along the posterior midline are most frequently affected. The mucosa is edematous and thickened, and small tubercles form in the submucosa. With increase in size and caseation the surface is ulcerated.

Clinicopathologic Correlation. Ulceration in any part of the respiratory tract is responsible for pain. Involvement of the vocal cords

leads to hoarseness and aphonia, the most common symptoms of laryngeal tuberculosis. Encroachment on the epiglottis and fibrosis of the glottic spaces are the cause of the dysphagia (Myerson).

TUBERCULOSIS OF THE GASTRO-INTESTINAL TRACT

Secondary tuberculosis of the gastro-intestinal tract results from swallowing infected sputum in advanced pulmonary tuberculosis.

Buccal Cavity. Tubercles form in the lymphoid tissue of the mucosa and submucosa and subsequently ulcerate. The usual tuberculosis lesion of the tongue is a ragged ulcer at the base (Katz). In infection of the parotid gland the bacilli probably enter through the duct (Berman and Fein).

Esophagus. Tuberculosis of the esophagus is an unusual lesion, and arises by direct extension from tuberculosis of the mediastinum or by implantation on the mucosa of bacilli in swallowed sputum. The functional effect is stenosis (Guggenheim, Rotenberg, and Laff).

Tuberculosis of the Stomach. Tuberculosis of the stomach is extremely rare. The usual lesion is a small or large, indurated ulcer in the pyloric part of the stomach (Hartz and von der Sar).

Intestine. Tuberculosis of the intestine is a common complication of fatal pulmonary tuberculosis and is found in about 80 per cent of all cases. The first lesion is a small tubercle in a solitary or conglomerate lymphoid patch. With caseation, a small discrete ulcer forms (Fig. 132, A). The inflammation extends into the surrounding lymphoid tissue, and the ulcer enlarges and becomes ragged and undermined. Bacilli are carried by the submucosal lymphatics toward the mesentery, and a chain of small tubercles develops (Fig. 132, B). These ulcerate into the lumen, and the characteristic large, elongated ulcer at right angles to the length of the intestine appears. Extension to the serosa follows, and subserosal tubercles form to complete the picture. Perforation occurs in not over 4 per cent. The mesenteric lymph nodes contain tubercles and frequently caseous foci (Cullen; Brown).

Rectum and Anus. About the mucocutaneous junction there are three conditions caused by the tubercle bacillus: (1) perirectal ab-

scess; (2) fistula in ano; and (3) perianal ulcer. In all it is probable that the bacilli gain entrance through a small abrasion in the mucosa. The perirectal abscess is usually in the ischiorectal space. The perianal ulcer is superficial and spreads at the mucocutaneous junction. In all tuberculous lesions of the anus or rectum there is secondary infection.

Fistula in Ano. Only 5 to 10 per cent of all examples of fistula in ano are tuberculous. The bacteria penetrate through the crypts of

TUBERCULOSIS OF THE URINARY TRACT

Renal Tuberculosis. *Pathologic Anatomy.* The earliest grossly demonstrable lesion in renal tuberculosis is a tubercle on the side of a papilla, usually in the upper pole. The tubercle increases in size, undergoes caseation, and ulcerates into the renal pelvis. This produces a deformity which is frequently seen in contrast pyelograms. Progressive enlargement of the cavity follows spread in a centrifugal direction, especially toward the capsule. The

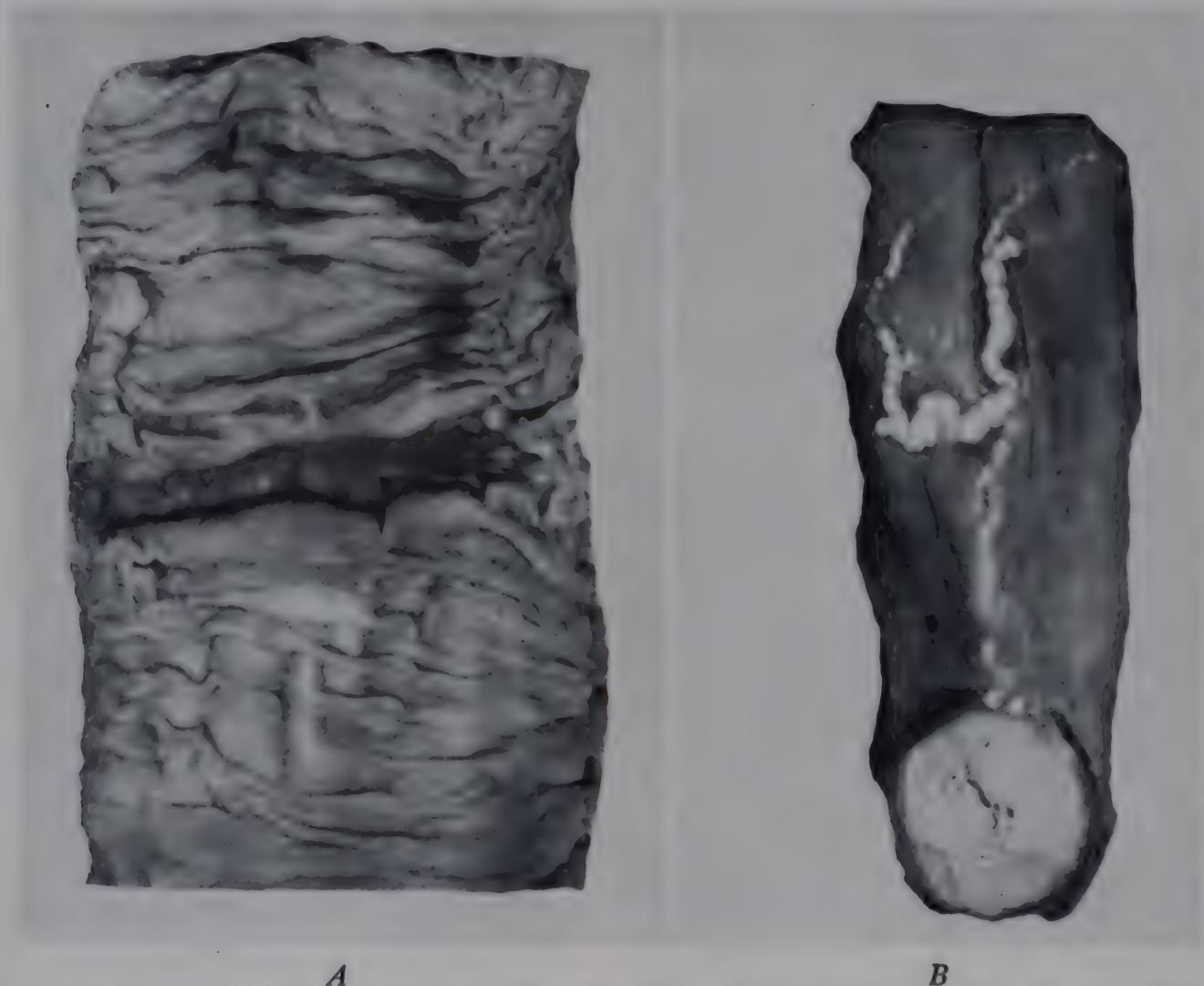


Fig. 132. Tuberculosis of intestine. *A*, Mucosal surface, showing ulcer across the intestine. *B*, Serosal surface, showing chain of peritoneal tubercles leading to a caseous mesenteric lymph node. (Photographs by courtesy of Dr. Oscar Auerbach.)

Morgagni and reach the ischiorectal space. With enlargement of the abscess, there is perforation externally or into one of the adjacent hollow viscera. The cavity is filled with a thick sanguinopurulent fluid and lined by granulation tissue.

Peritoneum. Tuberculosis of the peritoneum may follow rupture of a tuberculous mesenteric lymph node, may be associated with a tuberculous enteritis, or may originate by hematogenous dissemination. Small tubercles develop on the peritoneal surface, and dense fibrous adhesions unite the loops of the intestine. In locules between the adhesions there is cloudy fluid.

caseous material discharged into the pelvis bathes the other papillae, and similar lesions are formed in other parts of the kidney. Microscopic study of the cavity shows an inner lining of caseous material, a midzone of tuberculous granulation tissue with tubercles, and an outer zone of compressed renal substance, fibrosis, and lymphocytic infiltration.

Further change depends on concomitant disease of the ureter. If the ureter is partially blocked, hydronephrosis develops and the tuberculous cavities and intervening renal substance are compressed against the capsule. If the ureter is completely occluded, the greater part of the kidney undergoes caseation and

liquefaction. The result is a thin-walled sac, filled with yellow, thick pus. Microscopic examination shows the lesions of both tuberculosis and hydronephrosis.

Pathogenesis. As with all other types of organ tuberculosis, bacilli may reach the kidney by the blood, by the lymph, or by direct extension, but most renal tuberculosis is hematogenous. Bacilli pass through the glomerulus, down the tubule, and lodge in crevices about the papillae.

tuberculous ulcers of the mucosa rapidly spread to involve the entire mucosa and penetrate to the submucosa. The result is a dilated, thick-walled ureter, lined by tuberculous granulation tissue. Excessive fibrosis in focal regions may produce stenosis. In the obstructive type the lumen in a focal region or throughout is filled with caseous material. The ureter appears as a cylindrical structure, 5 to 8 mm. in diameter, composed of a dense fibrous wall, enclosing a central caseous core.

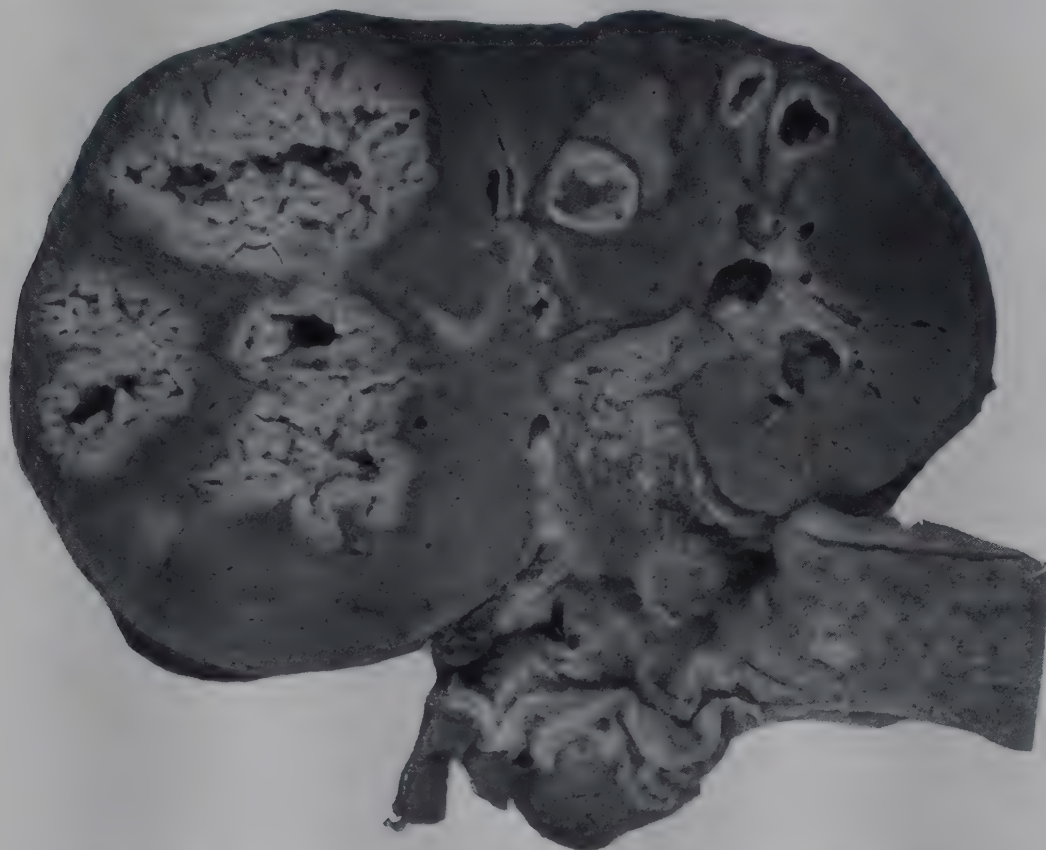


Fig. 133. Tuberculosis of kidney, renal pelvis, and ureter.

Clinicopathologic Correlation. Renal tuberculosis is primarily a disease of one kidney (85 per cent). It occurs in both men and women between the ages of thirty and fifty years. The inflammation of the kidney is reflected in the presence of pus cells in the urine, and irritation of the bladder is responsible for the dysuria. The course of the disease is chronic. Careful anatomic studies (Lieberthal and Húth) and experimental investigations (Ordway and Medlar) show lesions of the kidney in every case in which tubercle bacilli are present in the urine.

Descending Urinary Tuberculosis. Descending urinary tuberculosis is a proved entity. Bacilli discharged into the pelvis pass with the urine through the lumen of the ureter and bladder and lodge in the clefts of the mucosa.

Ureteral Tuberculosis. Two types of ureteral tuberculosis are recognized—ulcerative and obstructive. In the ulcerative form, small

Tuberculosis of the Urinary Bladder. The initial lesion is a tubercle in the mucosa, usually adjacent to the ureteral orifice draining a tuberculous kidney. Ulceration and confluence of ulcers follow to form a large focus, covered with caseous material. Fibrosis in the wall results in contraction of the bladder and the inevitable clinical symptom of this pathologic change—frequency and urgency of urination.

Miliary Tuberculosis in Urogenital Tuberculosis. Miliary tuberculosis and tuberculous meningitis are more commonly associated with urogenital tuberculosis than with any other form of extrapulmonary organ tuberculosis. The onset frequently follows nephrectomy or vigorous massage of the prostate.

TUBERCULOSIS OF THE GENITAL ORGANS

In fatal tuberculosis there are lesions of the genital organs in about 12 per cent of cases (Auerbach).

Pathologic Anatomy. The first discernible lesion is usually a small tubercle in the interstitial tissue. The tubercle grows by the formation of daughter tubercles; and as the surface is reached, the epithelium is destroyed and the lumen fills with caseous material.

In the developed stage the organ is enlarged and firm. On the cut section caseous foci and miliary tubercles are seen. In a hollow viscus the lumen and the inner part of the wall are converted into a homogeneous, caseous mass, surrounded by a thin, dense, fibrous capsule. The caseous foci may ulcerate into a larger hollow viscus, and single or multiple, ragged cavities may result. Healing is to be recognized by excessive fibrosis and calcification.

sociation with some other primary focus in the body.

Tuberculosis of the Male Genital Organs. Of all examples of male genital tuberculosis the prostate is involved in over 90 per cent, and in one-third is the only genital organ with tuberculosis. Seminal vesicles and epididymides are involved in about half, while the testis rarely shows lesions except miliary tubercles.

Tuberculosis of the Female Genital Organs. The fallopian tubes are involved in over 90 per cent of all examples of female genital tuberculosis. In early stages there are miliary tubercles in the wall, while in late stages the tube is an elongated, circular, caseous mass,

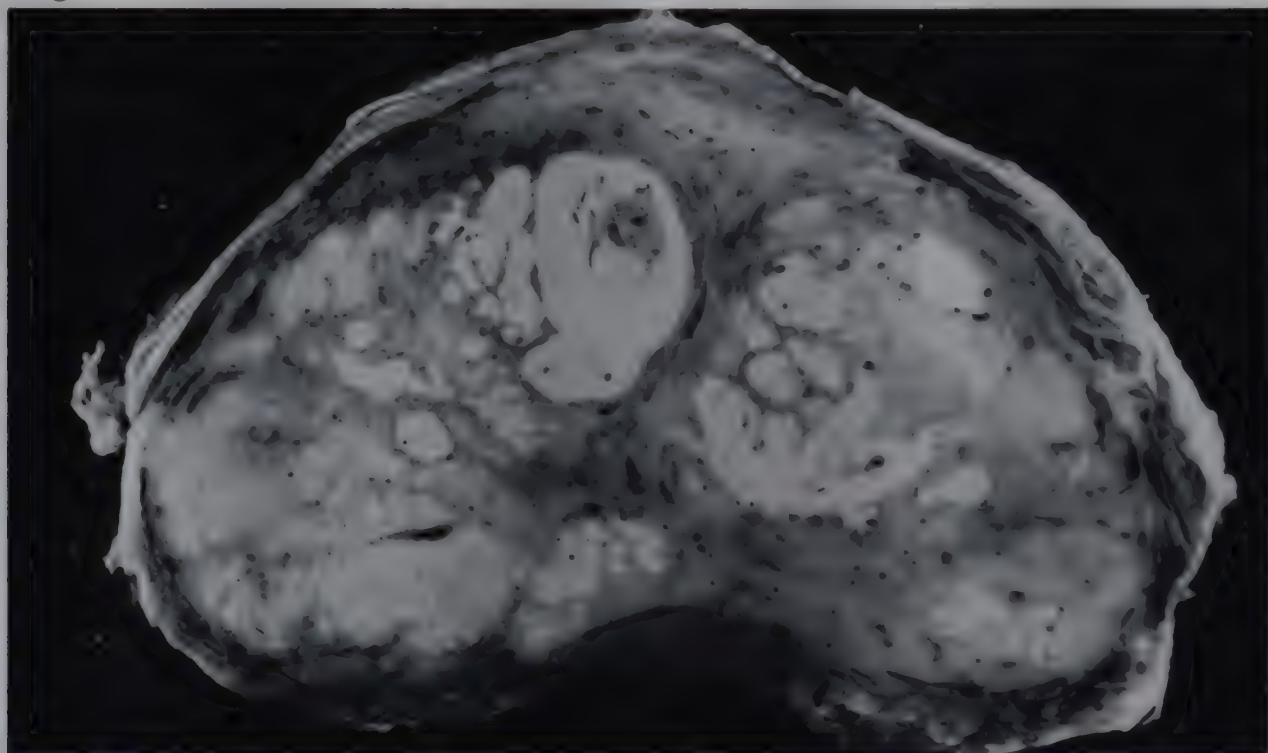


Fig. 134. Tuberculosis of prostate.

Pathogenesis. From a logical standpoint the tubercle bacilli may reach the genital tract in any one of three ways: directly from the outside, by extension from surrounding organs through tissue or along hollow viscera, and by the blood. Primary genital tuberculosis is extremely rare. Direct extension, from the epididymis to the prostate or from the prostate to the epididymis, along the vas deferens, has also been shown to be rare (Moore and Smith). On the other hand in tuberculosis of the female genital organs direct extension from tube to ovary and tube to endometrium seems possible.

Most evidence favors hematogenous dissemination as the usual source of the bacilli in genital tuberculosis. The initial lesion is an interstitial tubercle, and there is constant as-

sociation with some other primary focus in the body.

TUBERCULOSIS OF BONES AND JOINTS

The more important sites for tuberculosis of bone are the spine, the hip joint, long bones of the extremities, knee joint, sacro-iliac joint, sternum, elbow joint, ribs, and shoulder joint.

Tuberculosis of Bone. Tuberculosis of bone is essentially a destructive disease. Tubercle bacilli brought by the blood lodge in the capillaries of all parts of the bone, but most frequently in the epiphyses. Tubercles develop and enlarge. There is caseation and destruction of the spongiosa. Disintegrating trabeculae are surrounded by caseous tissue

or by a grayish red fleshy tissue, set through with tubercles. In the usual type, the disease is in the metaphyseal region. The end of the bone is uniformly enlarged and covered by irregular trabeculae of periosteal bone (Fraser, Meng and Wu).

Tuberculous Spondylitis (Pott's Disease).

One of the most common sites of tuberculosis of bones and joints is the vertebral column. So far as can be determined by serial studies, tuberculosis of the vertebra may be of three types: (1) central, (2) intervertebral, and (3) anterior (Doub and Badgley).

tuberculosis of the spine, the infection spreads into the paravertebral tissues. In tuberculosis of the cervical vertebra, the abscess commonly points into the retropharyngeal region, and may by pressure produce stenosis on the pharynx. From the upper dorsal region, the abscesses are directed into the posterior mediastinum. In the lower dorsal and lumbar regions, the abscesses generally enter the sheath of the psoas muscle.

The abscesses show little clinical evidence of inflammation, and the lack of increased temperature of the part is the basis for the



Fig. 135. Tuberculosis of spine.

After the infection is established in any type, there is replacement of the marrow with tuberculous tissue, destruction of bone and cartilage, and spread into the posterior and anterior ligaments (Cohn). Tuberculous spondylitis is a disease of children and of adults up to forty years.

Kyphosis. The destruction of one or more vertebral bodies and collapse of the column at this point lead to the characteristic angulation of the back with the convexity posteriorly—kyphosis or “hunchback.” The deformity is most prominent in the dorsal regions where there is a normal posterior curvature.

Paravertebral Abscess. In most cases of

name “cold abscess.” The cavity is filled with a thick yellow fluid and the walls are composed of an inner layer of caseous material and an outer layer of tuberculous granulation tissue. In healing, large masses of calcium may be deposited.

Extradural Abscess. In about 10 per cent of patients with tuberculous spondylitis, there is spastic paralysis of the lower extremities, indicating compression of the spinal cord. Correlated studies show that this is associated with the formation of an extradural tuberculous abscess.

Tuberculous Arthritis. Tuberculous diseases of joints may begin by extension from tuberculosis of adjacent bone or as an inde-

pendent tuberculous synovitis. In both instances, seeding of the synovial fluid with tubercle bacilli rapidly leads to the formation of tuberculous granulation tissue over the entire synovial space. With further progress the granulation tissue grows into the cavity and covers the cartilage where it is not in immediate apposition with the opposing cartilage. Interference with nutrition of the cartilage by the pannus and direct erosion soon result in loss of cartilage. At the same time, there is proliferation of granulation tissue in the sub-

The systemic effects of the tuberculous infection are the same as in any other variety of tuberculosis. The local changes in the bone are related to inflammation and to destruction of the joint or bone.

TUBERCULOSIS OF THE CENTRAL NERVOUS SYSTEM

Tuberculosis of the central nervous system occurs most frequently in association with first infection tuberculosis. The lesions of the brain and spinal cord are of two types: a diffuse or

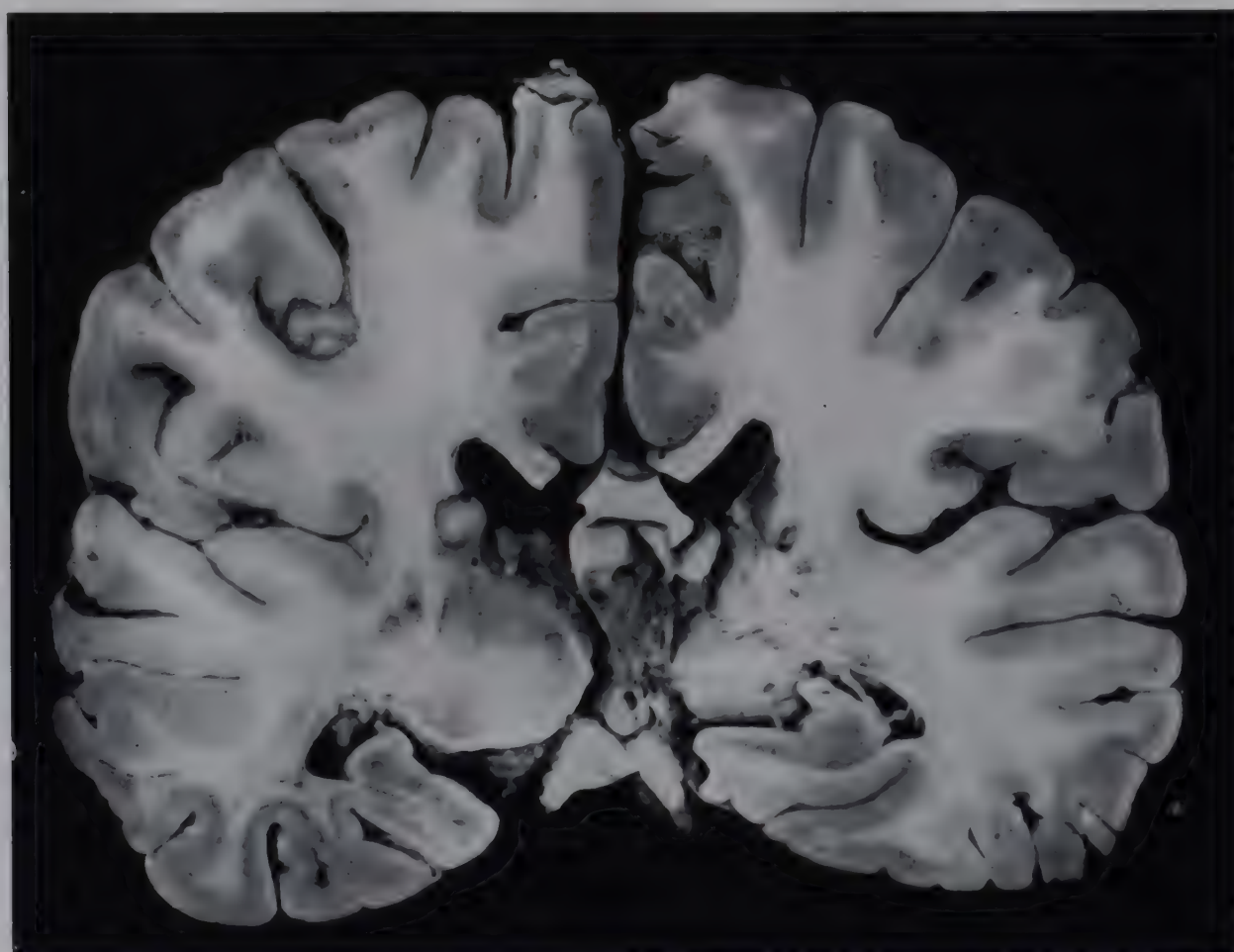


Fig. 136. Tuberculoma of brain adjacent to ependyma of lateral ventricle.

chondral tissue, destruction of bone and loosening of the cartilage. The loosened cartilage undergoes resorption slowly. Finally there is invasion of the end of the bone by the tuberculous infection with caseation and formation of sequestra, especially under regions bearing weight (Phemister and Hatcher).

Clinicopathologic Correlation. Tuberculosis of the bones and joints is secondary to a primary lesion in some other part of the body. About 60 per cent of cases are caused by bovine bacilli (Fraser). The progression of changes is accurately shown in radiographs. Subchondral resorption appears as a rarified zone; subchondral invasion as a dense, opaque, bone-free area; and resorption of cartilage as a narrowing of the joint space.

focal inflammation of the leptomeninges—tuberculous meningitis, and a local mass of tuberculous tissue within the substance of the brain or spinal cord known as “tuberculoma.”

Tuberculoma of the Brain. *Pathologic Anatomy.* The usual tuberculoma of the brain is a spherical nodule from 5 to 15 mm. in diameter, with an irregular outline, sharply demarcated from the surrounding tissue. The center is completely necrotic. At the edge there is a proliferation of fibroblasts, which are infiltrated with lymphocytes. Embedded within this fibrous wall there are typical tubercles, each with a central giant cell. In the immediately adjacent brain tissue there is proliferation of the astrocytes.

Clinicopathologic Correlation. Tuberculomas are most often single nodules. About one-half of all observed cases are in children less than ten years of age. They are space-consuming lesions, and therefore not infrequently come to the attention of the neurosurgeon. Unfortunately, most attempts to remove them result in the spread of the disease into the subarachnoid space, with death from tuberculous meningitis within a few weeks (Van Wagenen).

Tuberculous Meningitis. *Pathologic Anatomy.* The leptomeninges are greatly thickened,

of tuberculous meningitis are largely those of infection and of increased intracranial pressure. The mortality is 100 per cent.

TUBERCULOSIS OF THE CARDIOVASCULAR SYSTEM

Tuberculosis may involve the pericardium, myocardium, or endocardium, but tuberculous pericarditis is the commonest and is found in about 3 per cent of all autopsies on patients with active tuberculosis (Sweeney).

In the initial stages of *tuberculosis of the pericardium* the pericardial sac is filled with a serous or serosanguineous fluid, and the sur-

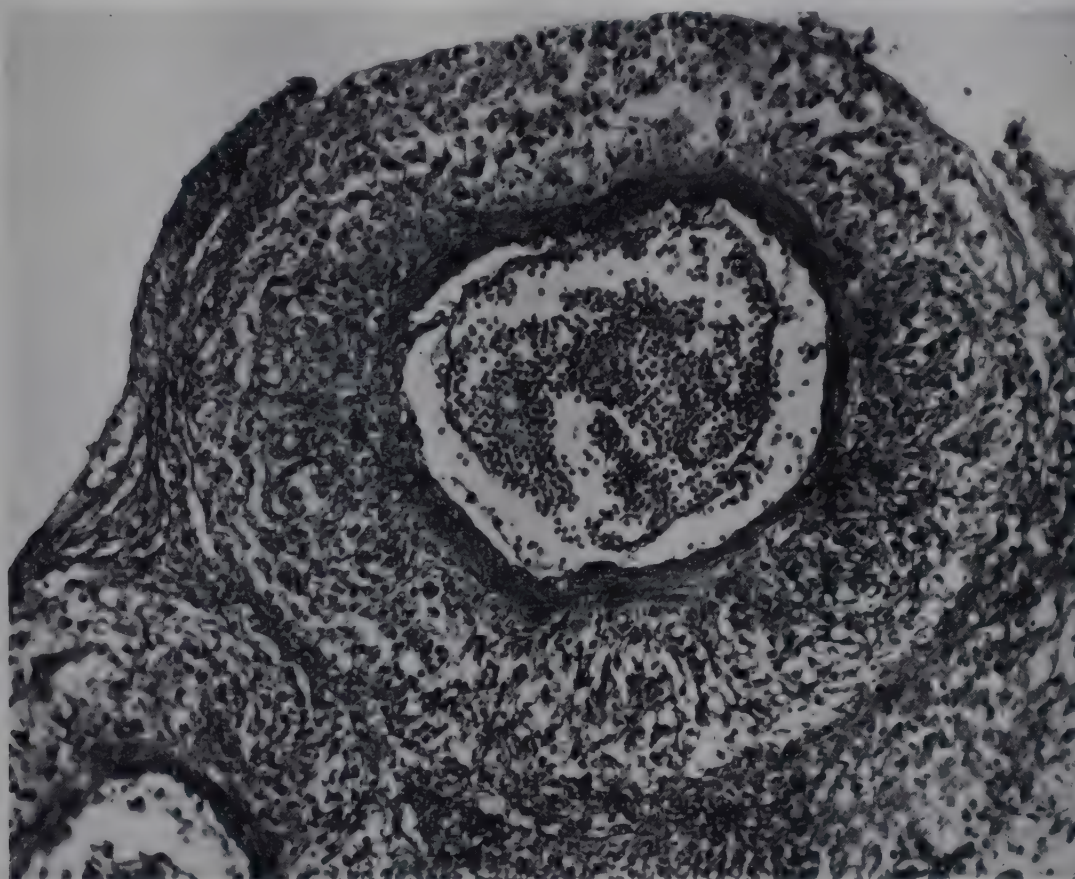


Fig. 137. Tuberculous granulation tissue about a pial blood vessel in tuberculous meningitis.

reddish gray, and translucent. In the thickened meninges and over the convexities, grayish white tubercles, almost 1 mm. in diameter, are visible. In the substance of the brain one or more tuberculomas are present. The most distinctive feature seen microscopically is the tuberculous granulation tissue radially arranged about the pial blood vessels (Fig. 137). In more extensive or older lesions there is caseation and invasion of the adjacent cerebral substance.

Pathogenesis. Rich and McCordock have postulated that a tuberculoma ruptures into the cerebrospinal fluid, seeds the leptomeninges, and thus produces meningitis. Other investigators have had less success in demonstration of the tuberculomas.

Clinicopathologic Correlation. The effects

of tuberculous meningitis are largely those of infection and of increased intracranial pressure. The mortality is 100 per cent. The pericardium progressively thickens, and adhesions form between the two layers, loculating the fluid and forming a dense membrane, 1 to 2 cm. thick. In almost all examples there is tuberculosis of the hilar nodes (Heimann and Binder). In some patients the accumulation of fluid in the pericardial sac may lead to signs of acute or chronic intrapericardial pressure (Beck and Cushing).

Tuberculosis of the myocardium may originate as an extension of tuberculous pericarditis, as conglomerate tubercles of a hematogenous spread, or as a diffuse interstitial myocarditis with infiltration of lymphocytes, mononuclear cells, and giant cells (Horn and Saphir).

Tuberculous endocarditis is rare (Baker; Bevans and Wilkins). *Tuberculous endarteritis* of the larger vessels usually results from erosion of a tuberculous node through the wall (Gross).

MISCELLANEOUS TUBERCULOSIS LESIONS

Eye. Tuberculosis of the eye, aside from miliary tubercles of the choroid, is difficult to establish. A number of lesions—phlyctenular conjunctivitis, iridocyclitis, and sympathetic ophthalmia—have been designated either tuberculous or tubercular, but bacilli are rarely if ever demonstrable (Bickerton).

Ear. Tuberculous otitis media and mastoiditis are characteristically associated with advanced pulmonary tuberculosis. The bacilli reach the middle ear by way of the eustachian tube. The cavity is filled with caseous material and granulation tissue, and there is a chronic discharge through a perforation in the tympanic membrane.

Lymph Nodes. Aside from those types which occur as a part of tuberculosis of single organs and systems, isolated tuberculosis of lymph nodes is rare. Not infrequently the lesions are strictly proliferative, without caseation, and the condition is known as "hyperplastic tuberculosis."

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XXVIII

Infections of the Eye and Accessory Structures

Bacteria may gain entrance to the eye by direct penetration from the outside—exogenous infection—or may be brought by the blood—endogenous or hematogenous infection. Since most of the specific bacterial diseases of the eye—conjunctivitis, iritis, etc.—are caused by many different bacteria, the following discussion is based on an anatomic classification rather than on a classification by cause.

Infections of the Eyelid

Hordeolum. The hordeolum or sty is a circumscribed, acute, suppurative inflammation of the glands of Zeis in the edge of the eyelid—external hordeolum; or of the meibomian glands in the tarsus—internal hordeolum. There is a red nodule with a yellow summit. There is the usual microscopic picture of suppurative inflammation and the cause is the staphylococcus. Both types are more common in younger persons and in those with refractive errors.

Blepharitis. Blepharitis is a chronic inflammation of the glands and tissues of the margins of the lids, which are swollen and red. There is scaling of the epidermis and loss of the lashes. Ulceration may be present, especially on removal of the scales. It is most common in children, and is seen as a sequela of the exanthematous diseases.

Orbital Cellulitis

Cellulitis of the orbit is usually secondary to inflammations of surrounding structures—sinusitis of the ethmoid, frontal, sphenoid, or maxillary sinuses, osteomyelitis of the frontal or maxillary bones, dental infections or infections of the region drained by the facial vein.

Pathologic Anatomy. The orbital tissues

are edematous and hyperemic. The individual elements are separated by a limpid or a thick cloudy fluid, with foci of necrosis and supuration. The veins and lymphatics are filled with thrombi, and an infected thrombus may extend posteriorly into the cavernous sinus.



Fig. 138. Orbital cellulitis. (Photograph by courtesy of Dr. Theo. Walsh.)

In those infections secondary to sinusitis, the infection spreads through sinus tracts, dehiscences of bone, or by propagation of a thrombophlebitis.

Bacterial Causes. The bacteria are those that cause the primary infection of the surrounding structures: the staphylococcus, streptococcus, and pneumococcus. Direct rupture of a dacryocystitis or of a subperiosteal abscess or osteomyelitis secondary to fracture or trauma accounts for a few cases. Metastatic abscesses of the orbit are rare.

Clinicopathologic Correlation. The accumulation of the inflammatory exudate in the limited space of the orbit pushes the eye forward—proptosis. The inflammation may extend to the lids, which become swollen and red, and to the conjunctiva—chemosis. Great increase of intra-orbital pressure may compress the optic nerve or the retinal artery and vein and thus lead to impairment of circulation in the retina and diminished visual acuity. As in all inflammations there is tenderness on pressure and a tendency to limit all voluntary movement—fixation, and pain on rotation.

Conjunctivitis

There are many causes of inflammation of the conjunctiva, and from a clinical standpoint there are numerous varieties. Perhaps the best classification is one based on the type of inflammatory reaction—catarrhal, purulent, membranous, necrotizing, granular, and phlyctenular.*

Acute Catarrhal Conjunctivitis. The conjunctiva of the eyelids and the retrotarsal fold, and to a less extent of the globe, is swollen and red, and the dilated vessels form a reticular pattern. Petechiae are occasionally present. In severe infections the cornea may be involved, with swelling and hyperemia of the eyelids. The conjunctiva is covered by an abundant fluid, either clear and limpid or thick and purulent, with suspended flakes of mucus and pus. The microscopic appearance is that of acute inflammation.

Causal Agents. Conjunctivitis is predominantly a bacterial disease, but a few examples are caused by foreign bodies and by viruses, as in the acute exanthemata. Cultures in the early stages yield, in approximate order of frequency, the diplobacillus of Morax-Axenfeld, the staphylococcus, *Corynebacterium xerosis*, the pneumococcus, bacilli of the genus *Haemophilus*, the streptococcus, and the gonococcus. In late stages cultures are frequently sterile. Pathologic changes in all are essentially the same. Most types are highly contagious and both eyes are affected.

Clinicopathologic Correlation. The usual duration of conjunctivitis is one to two weeks, but the inflammation occasionally be-

comes chronic. The swelling causes slight stimulation of nerves and consequent burning, smarting or itchiness, and hypersecretion by the lacrimal glands. Involvement of the cornea is associated with severe pain.

Keratitis

Keratitis, or inflammation of the cornea, is rarely a primary disease. Many examples are specific—the chronic interstitial keratitis of congenital syphilis and the acute keratitis of herpes simplex. Others are secondary to traumatic injury of the cornea or penetrating wounds of the anterior chamber; and still others are the result of the spread of infection from a conjunctivitis.

The inflammatory reaction in the cornea is of interest to the general pathologist because it represents, at least in the early stages, an inflammation in an avascular tissue (Adami). The vascular response to the irritant is in the nearest vessels of the conjunctiva. The cornea becomes cloudy or opaque because of the accumulation of cells and exudate. It is surrounded by a circle of dilated vessels. If healing is by organization and not by lysis, vessels and fibroblasts invade the cornea, and the result is a vascularized opaque membrane with partial or complete loss of vision.

Choroiditis—Retinitis— Panophthalmitis

Acute choroiditis may result from the entrance of bacteria through penetrating wounds or by the blood stream, as in septicemia and pyemia. Chronic choroiditis is usually specific and is related to tuberculosis, syphilis, or leprosy. A unique type is sympathetic ophthalmia, which is discussed in the chapter on diseases of the eye (p. 1001). Primary and isolated inflammations of the retina caused by pyrogenic bacteria are rare.

Panophthalmitis is an inflammation of the entire eye, and is usually secondary to penetrating wounds. There are edema and inflammation with polymorphonuclear leukocytes in all tissues, and the anterior and posterior chambers are filled with pus. As the inflammation subsides there is contraction of fibrous tissue, and a small, firm globe, with a wrinkled surface, is formed—phthisis bulbi.

* For a discussion of the specific conjunctivides, see the chapters on gonorrhea, diphtheria, plague, and tularemia.

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XXIX

Otitis Media, Complications and Sequelae. Brain Abscess

The middle ear is a small cavity drained only by a narrow, long tube. Aside from the thin tympanic membrane which separates it from the exterior, it is encased in a bone which shows a variable degree of pneumatization. Of importance in a study of the complications of otitis media is a recognition of the adjacent structures. In children after the age of two years the cavity of the middle ear is in free communication, through the antrum, with the cells of the mastoid. On the medial side it is separated from the cochlea by a thin membrane guarding the round window and from the vestibule by the bony foot plate of the stapes over the oval window. In a certain percentage of adults the greater part of the petrous portion of the temporal bone becomes pneumatized and these cells freely communicate with the cavity of the middle ear. Additional anatomic arrangements of interest to the pathologist and to the otolaryngologist are the pathway of the seventh nerve through the petrous bone, the canal of the carotid artery through the apex of the bone, the perineurial lymphatic spaces of the eighth nerve and the cochlear canal which join the fluid within the subarachnoid space with that within the internal ear, the immediate proximity of the superior, inferior, cavernous, and sigmoidal sinuses on the internal surface of the bone, and the presence of the sixth and fifth nerves and the gasserian ganglion over the apex of the petrous bone. Each of these structures may become involved in an inflammation starting in the middle ear and give rise to definite signs and symptoms. A final point is the closeness of the meninges and brain, which may be secondarily involved following inflammations within the petrous bone through dehiscence of a thin place of bone, or through the veins which drain inward and connect with the intracranial sinuses.

Otitis Media

Bacterial Causes. Streptococcus haemolyticus is the most common cause of otitis media and its complications. The next most common bacterium is Diplococcus pneumoniae, Type III. When age is taken into consideration, the streptococcus is most common during childhood and adult life, but after fifty the pneumococcus becomes the predominant organism (Vaheiri). In general the two organisms produce with equal frequency such complications as labyrinthitis and thrombophlebitis, but the pneumococcus is more likely to lead to intracranial complications such as epidural abscess and leptomeningitis. The mortality rate from pneumococcal infections is distinctly higher than that from streptococcal infections.

Most examples of otitis media follow some inflammation of the upper respiratory tract, and the bacteria probably reach the cavity of the middle ear through the eustachian tube. Influenza and the common cold account for about half of the cases, but of importance in children are the inflammations following scarlet fever, measles, and mumps.

✓ **Pathologic Anatomy.** The cavity of the middle ear is lined by cuboidal epithelium, supported on a thin layer of delicate connective tissue. In acute inflammations there are hyperemia and edema of the mucosal lining, so that it becomes two or three times thicker than the normal. Into this edematous tissue are infiltrated numerous polymorphonuclear leukocytes which migrate through the epithelium and form a purulent fluid that fills the cavity. The tympanic membrane is composed of a dense collagenous connective tissue. With swelling about the orifice of the eustachian tube there is closure of the lumen, and the exudate accumulates under pressure within the

middle ear. This may result in bulging of the tympanic membrane toward the external auditory canal. Pus is also forced back into the pneumatized portion of the petrous bone and sets up an inflammation in these regions. Large numbers of leukocytes and fibrin tend to collect about the round windows at the foot plate of the stapes. Following spontaneous or operative perforation of the tympanic membrane, the pressure is relieved and, if the defenses of the body are adequate, there is resolution of the inflammatory process. Any residual exudate undergoes organization, with subsequent thickening of the mucous membrane at that point. In some chronic cases, in which the per-

changes are probably of the same order as those in the lung when amniotic fluid and squamous epithelial cells partially fill the alveoli. As in the lung, there may be secondary bacterial infection with a true suppurative otitis media (Hemsath).

Clinicopathologic Correlation. For proper function of the internal ear in the perception of sound, the eustachian tube must freely communicate with the posterior nasopharynx, the tympanic membrane must be under proper tension, and the three ossicles of the ear must move without restriction and delicately articulate into the oval window. In acute otitis media there is interference with all three of

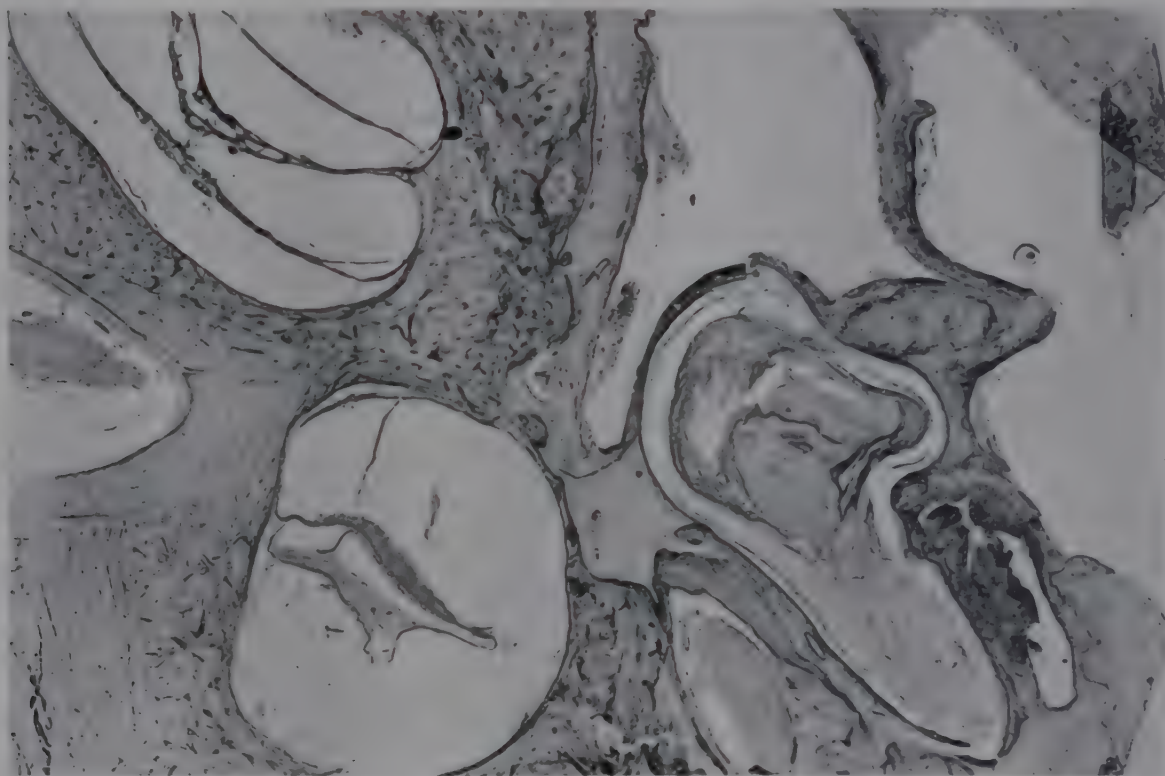


Fig. 139. Epidermoid cyst of the middle ear. (Tissue by courtesy of Dr. Theo. Walsh.)

foration in the membrane persists for long periods, the squamous epithelium lining the external auditory canal grows into and lines a part of the cavity of the middle ear and forms the cholesteatoma (Tumarkin). The squamous epithelium continues to grow, keratinizes, and desquamates into the artificial cavity. The chronic infection results in the formation of a thin or slightly cloudy fluid within the cavity, and fibrosis and lymphocytic infiltration in the wall (Semenov).

Otitis Media in the Newborn. In an occasional newborn child histologic examination of the middle ear will show that the cavity is filled with desquamated epithelial cells and that the mucosa is slightly edematous and infiltrated with lymphocytes and polymorphonuclear leukocytes. Bacteria cannot be demonstrated in this type of lesion. The pathologic

these: the eustachian tube is closed, the drum-membrane is under tension, and the ossicles are bathed in pus. Necrosis is seen frequently in the membrane of the round window and in the annular ligament of the stapediovestibular joint. If any of this exudate is organized, it will bring about complete or partial immobilization of the apparatus for conducting the sound waves from the air to the lymph within the labyrinth. In severe inflammations there may be necrosis of one or more of the ossicles, with complete or partial conduction deafness in that ear. The tension on the tympanic membrane results in excruciating pain, as does tension on all innervated tense membranes. The closure of the eustachian tube is responsible for the peculiar feeling, similar to that experienced when riding in an elevator. The inflammation in the tympanic membrane is

responsible for the red, bulging appearance of the drum membrane when viewed through the external auditory canal.

COMPLICATIONS

Mastoiditis. The cavity of the middle ear communicates through the aditus ad antrum with the air cells within the bone of the mastoid tip. Inflammations in the middle ear spread within the mucous membrane or in the lumen into these air cells. An exudate of fluid and polymorphonuclear leukocytes is poured into the mucous membrane and into the lumen, and unless properly and quickly drained the inflammation spreads into the surrounding bone and sets up an osteitis or an osteomyelitis. Necrosis of the thin membrane of bone separating the mastoid cells from the cranial cavity allows the infection to spread and produce an epidural abscess, thrombophlebitis of the dural sinuses, leptomeningitis, or abscess of the brain. The seventh nerve courses in a canal close to the mastoid cells. The inflammation may involve the perineurium or endoneurium of this nerve, with partial or complete loss of function—facial paralysis. Paralysis also occasionally results from operative trauma to the nerve during a mastoidectomy.

Apicitis. In some persons the pneumatization of the petrous part of the temporal bone takes in the greater part or all of the petrous pyramid, so that there are air cells about the carotid canal and immediately beneath the gasserian ganglion. Inflammations of the middle ear or of the mastoid may spread to these cells. The inflammation in these apical cells is similar to that in the middle ear and in the mastoid (Kopetsky and Almour). Dehiscence superiorly leads into the middle cranial fossa. Perforation in the immediate neighborhood of the fifth and sixth nerves frequently gives rise to Gradenigo's syndrome, which is paralysis of the sixth nerve and parietotemporal or supra-orbital pain (Greenfield). In the absence of pneumatization, an inflammation of the petrous pyramid takes on the usual characters of an osteomyelitis. Dehiscence into the carotid canal may induce an acute arteritis, with thrombosis or rupture of the carotid artery or of the accompanying veins.

Labyrinthitis. Labyrinthitis is an inflammation of the internal ear. It may involve the cochlear part or the vestibular part or both. The inflammation in the middle ear spreads

to the labyrinth through the round window, through the oval window (stapediovestibular articulation), or through the fissure ante fenestram. The lining membrane of the labyrinth shows the usual changes of acute inflammation: hyperemia and infiltration with leukocytes. If the inflammation results in destruction of cells of the organ of Corti or of the hair cells in the ampullae of the semicircular canals, there will be permanent loss of function, either hearing or equilibration. In the reverse direction a meningitis may bring

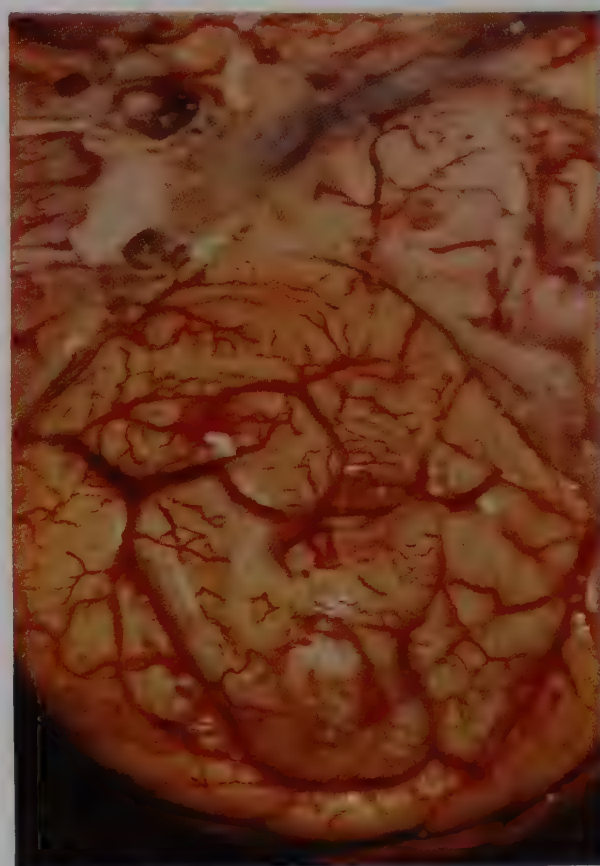


Fig. 140. Leptomeningitis and abscess of temporal lobe of brain secondary to otitis media. (Photograph by courtesy of Dr. Theo. Walsh.)

about a labyrinthitis by spread of the bacteria by way of the perineurial lymphatic spaces of the auditory nerve, by the perivascular spaces of the modiolar vessels, or through the cochlear aqueduct (Crowe).

Thrombophlebitis. From the petrous bone, particularly from the region of the mastoid, there are numerous small veins which empty into the dural sinuses. Inflammation within the petrous bone drains through these veins, and either a phlebitis or a thrombophlebitis of the veins may spread into the superior or inferior petrosal sinus or into the sigmoidal sinus, and thence to the jugular bulb and jugular vein. Under these conditions, small infected emboli are liberated and set up secondary multiple abscesses in the lungs, unless

the jugular vein is ligated. Direct spread of the infection through a dehiscence leads to a similar thrombophlebitis. In the case of an apicitis this involves the pericarotid venous plexus with subsequent involvement of the cavernous sinus, with all of the secondary changes of occlusion of the cavernous sinus in the drainage of the ophthalmic vein. Lesions of the sinuses are more frequent on the right side than on the left and are often associated with poor pneumatization of the petrous bone (Greenfield).

Inflammation of the Meninges. If the inflammation spreads by dehiscence, the dura mater is lifted from the surface of the petrous bone, and there is a local accumulation of pus, known as an epidural abscess. Perforation through the dura results in a subdural abscess or, if it is more generalized, an internal suppurative pachymeningitis. Further spread to the subarachnoid space leads to a leptomeningitis, either localized or diffuse (Williams, Herrell, Brown, Kernohan, and Wagner). About 2.2 per cent of all individuals with otitis media have an intracranial complication (Fig. 140).

Abscess of the Brain in General. Abscess of the brain may develop in a number of ways: (1) extension to the cerebral substance from the surrounding tissues, (2) localization from the blood, and (3) direct penetration of bacteria through an open fracture of the skull. In the first category are the abscesses secondary to otitis media, mastoiditis and thrombophlebitis of the dural sinuses; secondary to infections of the accessory nasal sinuses, especially the ethmoid and sphenoid; and secondary to osteomyelitis of the skull (Eisenstein, Friedman, and Davison). The abscesses are usually solitary and the localization is in direct continuity with the primary lesion (Sachs).

Hematogenous abscesses of the brain are usually multiple, and in most instances are secondary to suppurative disease of the lung or pleura (Buxton and White). The pathologic anatomy is similar to that of abscesses in other organs. It has been postulated that the bacteria go from the pleura to the brain through the vertebral system of veins. An association with congenital heart disease has also been noted (Smolik, Blattner, and Heys).

Otitic Hydrocephalus. In an occasional pa-

tient with otitis media without apparent spread of the inflammation to the cranial cavity, an acute hydrocephalus develops. The mechanism is not known, but the increase of pressure is only temporary and drainage of the fluid affords complete relief.

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Endocarditis

There are two general parts of the endocardium: that of the valves—valvular endocardium; and that over the cavities—mural endocardium. It is customary to use the unqualified term “endocarditis” to designate inflammation of the valvular endocardium, and to apply the qualified term “mural endocarditis” to inflammations of the nonvalvular endocardium.

General Classification. In many cases a definite bacterium can be isolated from lesions of the endocardium. In others bacteria cannot

Many other terms have been used, such as “malignant endocarditis,” “ulcerative endocarditis,” and “vegetative endocarditis,” but they serve little purpose.

The Bacterial Causes of Endocarditis. Thayer’s compilation (Table 14) of the bacterial causes of endocarditis will serve as a general guide. Among the streptococci, the hemolytic streptococcus is the more usual cause of acute bacterial endocarditis, while *Streptococcus viridans* is usually associated with subacute bacterial endocarditis. All bac-

TABLE 14. BACTERIAL CAUSES OF ENDOCARDITIS

Organism	Cases	Per Cent
Streptococcus	242	60
Pneumococcus	65	16
Staphylococcus aureus	53	13
Gonococcus	29	7
Influenza bacillus	13	3
Staphylococcus albus	5	1

be demonstrated, not necessarily because bacteria are not present, but because present methods are inadequate. Still other endocarditides are caused by the spirochete of syphilis. The following classification, first proposed by Gross, seems most satisfactory:

- I. Bacterial endocarditis (bacteria cultivated consistently from the blood during life or from the vegetations at autopsy)
 - (A) Acute bacterial endocarditis
 - (B) Subacute bacterial endocarditis
 - 1. With bacteremia
 - 2. In the bacteria-free stage
- II. Nonbacterial endocarditis
 - (A) Rheumatic endocarditis
 - (B) Atypical verrucous endocarditis
 - (C) Nonbacterial thrombotic endocarditis
- III. Syphilitic endocarditis (involving only the aortic valve).

teria have occasionally been incriminated as the cause of acute bacterial endocarditis. The more important, in addition to those listed, are *Salmonella* (Wells), *Brucella* (Levy and Singerman), and the meningococcus (Master).

General Pathologic Changes. Secondary Changes. Embolism. The characteristic pathologic change of acute endocarditis is the presence, on the atrial surface of the atrioventricular valves, or on the ventricular surface of the semilunar valves, at the line of closure, of a vegetation. In particular instances, especially in rheumatic endocarditis and in subacute bacterial endocarditis, these vegetations are also found on the atrial wall above the mitral valve, on the chordae tendineae of the atrioventricular valves, and on the ventricular

surface of the mitral and tricuspid valves. In acute bacterial endocarditis the vegetations are large and friable. In subacute bacterial endocarditis they are large but firm. In rheumatic endocarditis the vegetations are small and firm, and are frequently referred to as verrucae, because of their resemblance to warts.

Microscopically the vegetations in acute bacterial endocarditis consist of three distinct

clear leukocytes and red blood cells are entangled. In subacute bacterial endocarditis the vegetation is similar, but the peripheral part of the first zone is composed of young fibroblastic tissue and capillary vessels, indicative of organization (Moore).

It is at times difficult to distinguish between acute and subacute bacterial endocarditis. From a clinical standpoint it may be said that any endocarditis lasting longer than eight

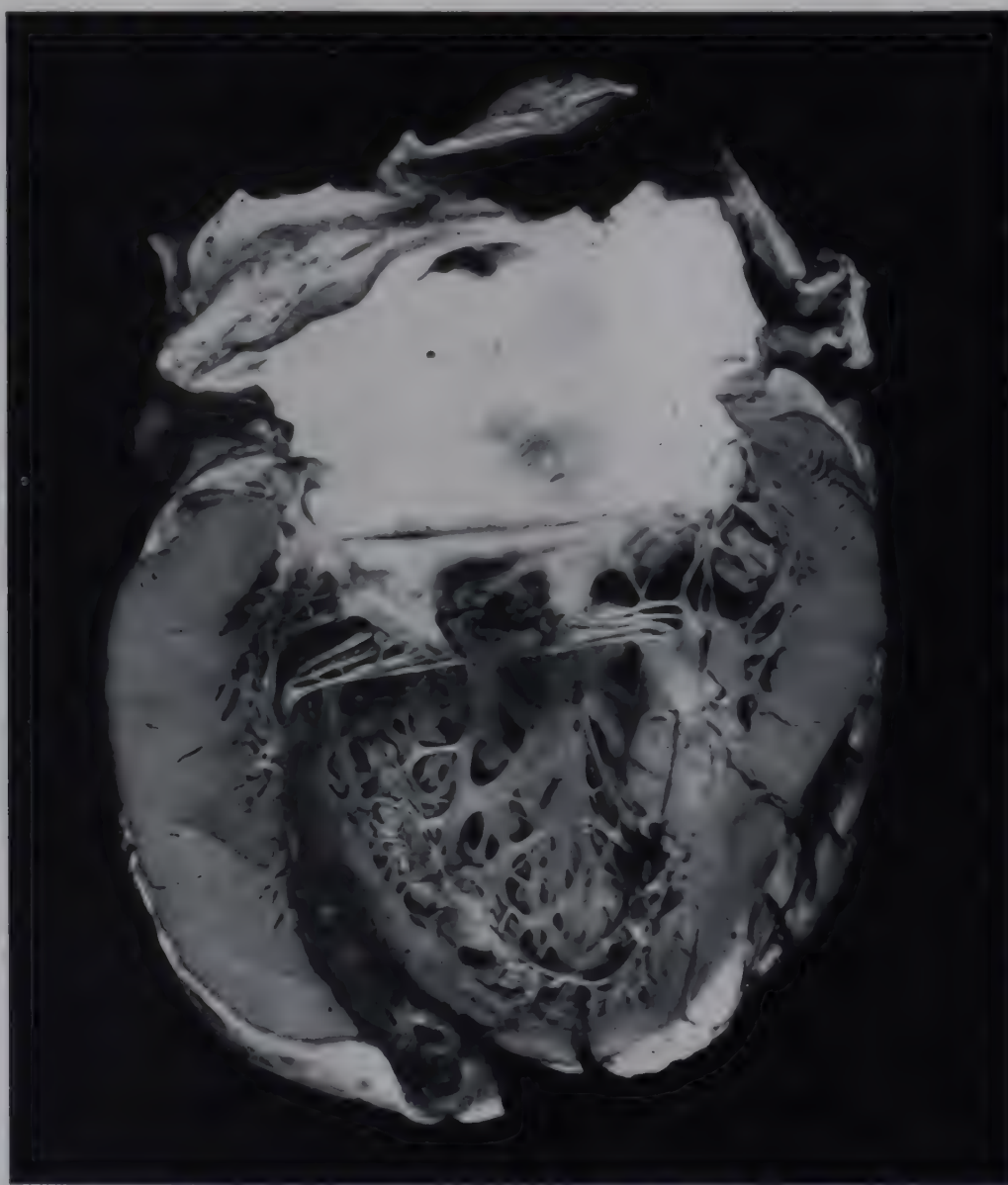


Fig. 141. Acute bacterial endocarditis of mitral valve.

zones. Immediately adjacent to the valve there is a zone, making up from one-half to three-fourths of the vegetation, composed of necrotic debris with few living cells. By special stains fibers of collagen and remnants of elastic fibrillae may be demonstrated. Some have taken this as evidence that this part of the vegetation is in reality necrotic valvular tissue, and not necrotic fibrin (Allen). The second zone, completely covering the first, is a relatively narrow rim of fibrin in which colonies of bacteria are embedded. The superficial third zone is composed of fibrin in which a moderate number of polymorphonu-

leucocytes are embedded. From a pathologic standpoint it is better to reserve this term for the endocarditides showing partial organization of the vegetation. In rheumatic endocarditis the greater part of the verrucae is made up of hyalinization and necrosis of the superficial valvular tissue, and the fibrin on the surface is minimal in amount. There are of course no bacteria. The pathologic changes of atypical verrucous endocarditis and of nonbacterial thrombotic endocarditis are characteristic, and will be described in sections devoted to each. In addition to the vegetation, the valvular tissues

show edema and cellular infiltration, indicative of a diffuse inflammation. In the valvular rings there is also inflammation, especially in the rheumatic type. In general, acute bacterial endocarditis is a monovalvular lesion, while rheumatic endocarditis is a polyvalvular lesion. Changes in the other viscera in large part depend on the source of the endocarditis, the character of the vegetations, and the specific bacterium responsible. In acute bacterial endocarditis with large, friable vegetations, systemic embolism is common. Infarcts of the spleen, kidneys, and brain are frequently observed. At times these infarcts undergo suppuration with the formation of abscesses. In subacute bacterial endocarditis infarcts of the viscera are the rule, but the organisms are of low virulence, and the formation of the abscesses is unusual. In rheumatic endocarditis, the vegetations are small and infarcts are rarely seen (Clawson, Bell, and Hartzell).

Involvement of Individual Valves. In general the valves of the left side of the heart are far more frequently involved than those of the right side. The individual bacteria do show some predilection for different valves, as demonstrated in Table 15, made from a compilation of the literature. All figures are percentage involvement.

Nonbacterial endocarditides are overwhelmingly diseases of the left side of the heart, and especially of the mitral valve. Rheumatic fever in an active stage is a polyvalvulitis, involving to a certain extent all of the valves.

Preexisting Disease of the Heart. Pathogenesis. Vascularization of Normal Valves. Although there must at some time be a first

preexisting disease of the involved valve with healing. The frequency of this association in different types of bacterial endocarditis is shown in Table 17, compiled from published reports.



Fig. 142. Subacute bacterial endocarditis of aortic valve. Note large vegetation and thickening of valve.

These figures leave little doubt that the previously damaged valve is more susceptible to infection than is the normal valve. De-

TABLE 15. BACTERIAL ENDOCARDITIS

Valve	Strep. Haemolyticus	Strep. Viridans	Pneumo- coccus	Staphylo- coccus	Gono- coccus
Aortic	59	53	76	50	70
Mitral	76	82	50	43	37
Pulmonic	6	3	24	25	10
Tricuspid	20	8	4	4	12

infection of the valves of the heart, even casual study of a series of hearts with subacute or acute endocarditis reveals that in many cases the substance of the valve is thickened and fibrotic—in other words that there has been

termination of the reason for this involves a study of the pathogenesis of acute endocarditis. Are the bacteria deposited on the surface of the valve or are they carried into the valve in blood vessels? One group maintains that

the normal valves contain blood vessels (Wearn, Bromer, and Zschiesche), while another group believes that evidence of a pre-existing disease can be demonstrated in

of subacute bacterial endocarditis in hearts with congenital lesions. In an analysis of 555 instances of congenital cardiac disease of clinical significance Abbott found subacute

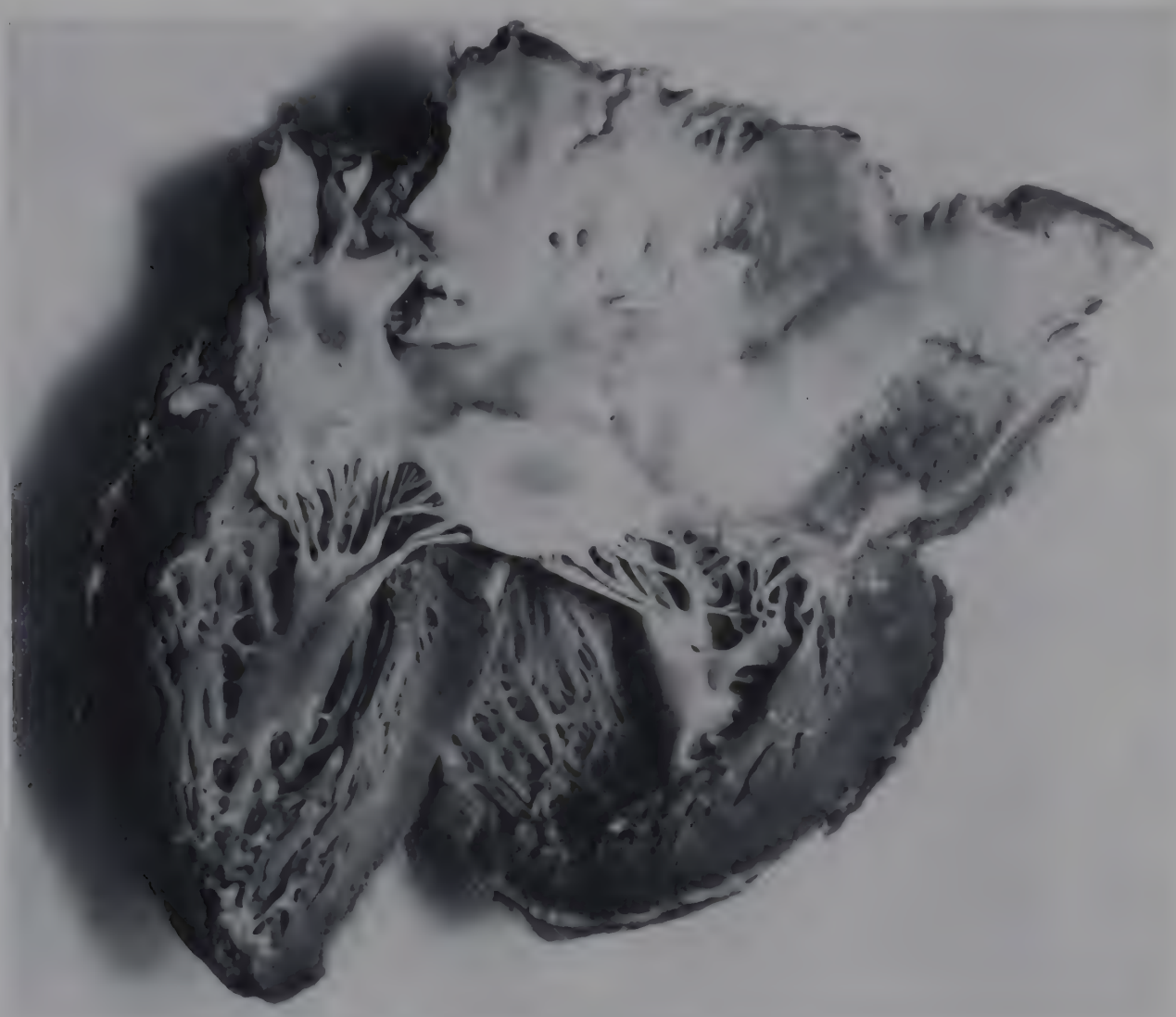


Fig. 143. Rheumatic endocarditis. (MacCallum.)

practically all vascularized valves (Gross). With precise criteria, however, the latter view is the more acceptable. The question then arises: do bacteria localize on the damaged

bacterial endocarditis in 17.6 per cent. The frequency with individual lesions was as shown in Table 18. The vegetations in these cases are on the thickened endocardium or

TABLE 16. NONBACTERIAL ENDOCARDITIS

Valve	Rheumatic		Atypical Verrucous	Thrombotic
	Verrucae in First Attack	Chronic		
Aortic	75	63	36	23
Mitral	92	73	100	98
Pulmonic	33	2	27	4
Tricuspid	66	10	64	11

valve because of injury to the thickened valves by the opposing valve and by the stream of blood flowing across them, or because of vascularization? Important contributory evidence is secured from a study of the incidence

the endocardium about the defect, where there is vascularization. However a careful analysis of the above lesions reveals that they all involve a mechanism whereby a stream of blood is forced through a small orifice. Further evi-

dence on this point is given by the report of cases in which a subacute bacterial endocarditis localizes on the mural endocardium at a point where a stream of blood strikes, after passing through a defect of the interventricular septum. The occurrence of subacute bacterial endarteritis about the orifice of an arteriovenous aneurysm further supports this view (Hamman and Rienhoff). Thus, with the

tic streptococcus may be the terminal event in a septicemia, or it may be a clinically recognizable complication of infections in other parts of the body. The most important of these are erysipelas, puerperal infections, infected fractures and wounds, and infections of the respiratory tract. Staphylococcal endocarditis is a complication of osteomyelitis, puerperal sepsis, and staphylococcal infections

TABLE 17. PREEXISTING DISEASE IN BACTERIAL ENDOCARDITIS

Organism	Per Cent on Valves with Preexisting Disease
Influenza bacillus	92
Subacute bacterial endocarditis, Streptococcus viridans	81
Streptococcus haemolyticus	70
Staphylococcus	41
Pneumococcus	35
Gonococcus	14

evidence at hand we may conclude that the valve with preexisting disease is more susceptible to infection because of the added damage to which it is subjected during systole of the heart. Part of the additional injury results from striking the opposing valve, and part from the rapid flow of blood across it. The presence of vessels within the damaged

of the skin. In only about 20 per cent of cases of subacute bacterial endocarditis caused by either Streptococcus viridans or the influenza bacillus is it possible to define the preceding disease or the portal of entry. In these the most frequent preceding event is a respiratory infection or the extraction of an infected tooth.

TABLE 18. CONGENITAL LESIONS IN SUBACUTE BACTERIAL ENDOCARDITIS

Lesion	Per Cent with Subacute Bacterial Endocarditis
Fused semilunar cusps	45
Defects at the base of the intraventricular septum	40
Defects at the lower part of the interauricular septum	38
Subaortic stenosis	37
Pulmonary stenosis	23
Patent ductus arteriosus	22
Coarctation of the aorta	16

valve is of minor importance (Allen). The disease responsible for the preexisting fibrosis of the valves or of other structures is in most instances rheumatic fever.

Associated Disease. Portal of Entry. The valves of the heart are inside the body and it is apparent that bacteria must enter the body at some point and be carried to the heart by the blood. Pneumococcal and gonococcal endocarditis are in most instances a complication of lobar pneumonia and acute gonorrheal urethritis. Endocarditis caused by the hemoly-

Nonbacterial Thrombotic Endocarditis. In debilitated patients, especially older persons with cancer or congestive cardiac failure, there are small vegetations on the mitral or aortic valves. Microscopically, the lesion is focal degeneration of the valve with imbibition of fluid. There is no evidence of inflammation. It is possible that similar lesions occur during intercurrent illnesses and that healing of them results in Lambl's excrescences and in slight fibrosis of the leaflets (Allen and Sirota).

Changes in the Valves with Age. Sclerosis of the Mitral Valve. Calcification of the Mitral and Aortic Rings. With increasing age the spongiosa of the valves becomes more dense, and richer in elastic tissue. The spongiosa in the ring and that near the attachment of the chordae tendineae of the atrioventricular valves becomes loose and is infiltrated with fat. The elastic fibers become more numerous and larger. The endocardium covering the valves becomes denser, thicker, and more collagen-

calcification of the mitral ring and of the bases of the aortic valves. It was originally postulated that this was the mechanism of formation of the calcified aortic valve with stenosis, but most instances of calcific aortic stenosis are now believed to be caused by rheumatic fever (Mönckeberg; Sohval and Gross; Fertman and Wolff).

Related Lesions. Lambl's Excrescences. On the aortic valve in the region of the corpora arantii, and less commonly on other valves,

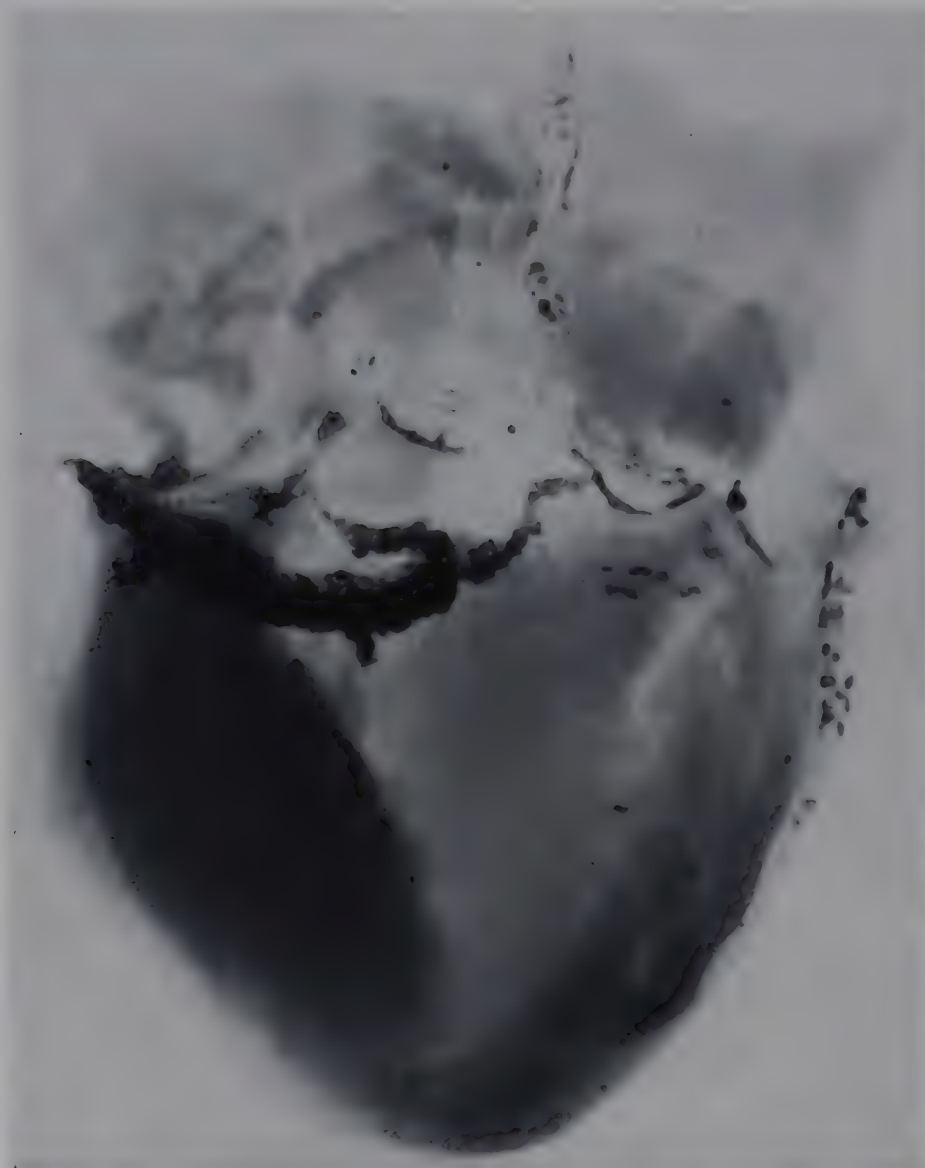


Fig. 144. Calcification of the mitral and aortic valvular rings.

ous, and the fibrosa undergoes hyalinization and fatty degeneration. In the substance of the valve, particularly near the tip, the fibrosa undergoes a mucoid type of degeneration and stains with basophilic dyes. The fatty degeneration in the mitral valve and in the bases of the aortic valves constitutes the usual picture known as "sclerosis." It is a process similar to, but probably not identical with, arteriosclerosis. The basic change is in the fibrosa of the valves and not in the endothelium. If the fatty degeneration is conspicuous in the valvular rings it is frequently followed by calcification, giving rise to the picture of

small, polypoid or papillary projections are seen in from one-fourth to one-half of all adult hearts, known as Lambl's excrescences. Histologically they are composed of dense collagenous connective tissue and elastic lamellae, continuous with similar layers of the aortic valve. They may represent organized thrombi, minimal endocarditis, or the reaction of a valve to strain and tearing incident to normal function (Gunzel).

Noduli Albini. At the attachment of the chordae tendineae onto the atrioventricular valves, especially in children, the tissues may appear grossly edematous and translucent.

These lesions, known as noduli Albini, are of no clinical significance.

Blood Cysts of the Valves. In the hearts of newborn infants, especially on the mitral valve, small cystic spaces 1 mm. in diameter, filled with blood, may be found. The cavity is lined with endothelium, and the lining of the cyst is continuous with the endothelium covering the valve (Boyd).

Ecchymoses of the Endocardium. In a wide variety of diseases ecchymoses of the endocardium are found at autopsy. They may be associated with toxic injury, as in diphtheria; powerful contraction of the heart, as during exsanguinating hemorrhages; stimulation of the vagus; the administration of digitalis (Aschoff); or with injury from the passage of an embolus through the heart (Clark and Berger).

Fetal Endocarditis. In most instances of valvular stenosis and atresia of the newborn there is abundant evidence that the lesion results from defective development, but in an occasional case there is histologically demonstrable inflammation of the tissues of the valve and ring, and it is possible that an intra-uterine endocarditis may heal (Stohr).

Clinicopathologic Correlation. The clinical signs and symptoms of endocarditis may result from mechanical interference with the action of the heart, from infection, or from embolism. In acute and subacute endocarditis the damage to the valves and the presence of the vegetations rarely interfere with adequate functioning. Murmurs may be heard, but there is little evidence of chronic passive hyperemia of the lungs and viscera in these patients. In chronic endocarditis following repeated attacks of rheumatic fever the entire clinical picture depends on interference with the action of the valves, producing either stenosis or insufficiency. This topic is fully discussed in Chapter LXXXV, p. 721.

The evidences of infection are the usual ones—fever, leukocytosis, enlargement of the spleen and lymph nodes, and weakness. The phenomenon of embolism has been discussed. Infarcts are most common in the kidneys and spleen, but any structure in the body may be involved. When the emboli carry virulent bacteria abscesses may form. An acute arteritis or a mycotic aneurysm may be the sequela of embolism with less virulent bacteria.

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XXXI

Puerperal Infections

Pathologic Anatomy. Following delivery in a small percentage of women an inflammatory process develops in the uterus. The uterus in such a patient is large and shows less involution than normal. The endometrium is ragged, friable, and in large part necrotic, especially in the region of the placental site, where the

uterus is covered by a fine, fibrinous exudate, and there are pelvic abscesses in the parametrium or pelvic cavity. The larger veins in the broad ligament, particularly the uterine vein, are filled with a semiliquid, grayish yellow thrombus, indicative of a suppurative thrombophlebitis. In some cases the inflam-



Fig. 145. Puerperal metritis.

tissues are elevated, grayish yellow, and not infrequently hemorrhagic. The wall of the uterus is thickened and pus can be expressed from many of the blood and lymph vessels and from the interstitial spaces of the uterine wall. Many of the blood vessels and lymph vessels are filled with thrombi. The parametrium is edematous and hyperemic. If the process is extensive the peritoneum over the

mation of the peritoneum is more generalized. In many of the fatal cases there are infected emboli and abscesses in the lung.

Microscopically, the endometrium appears necrotic, with numerous bacterial colonies embedded in the necrotic tissue. The myometrium is edematous and the bundles of smooth muscle are widely separated. Within the edematous tissue there is a slight infiltra-

tion with mononuclear cells, lymphocytes, and a few polymorphonuclear leukocytes. The lymphatics are dilated and filled with similar cells, with or without a delicate fibrin thrombus. In many of the blood vessels there is leukocytic infiltration of the wall and the lumen is filled with a thrombus infiltrated with leukocytes. The thrombi in the uterine veins present a similar appearance. The abscesses in the lung and in the other solid viscera are identical with those found in other examples of pyemia.

Pathogenesis. Two bacteria are in large part responsible for puerperal infection, anaerobic streptococci and hemolytic streptococci.

In the days before Lister and Pasteur, puerperal infection was extremely common, especially in the clinics of Europe and in the home deliveries in the United States. Oliver Wendell Holmes and Ignaz Philipp Semmelweis first pointed out that in vaginal examination of the woman in labor the dirty hands of the doctors and midwives carried bacteria into the vagina and uterus and thus caused most cases of puerperal infection. Following acceptance of this viewpoint there was a precipitous fall in the incidence of the disease. With the discovery that many of the cases were caused by an anaerobic streptococcus, and that anaerobic streptococci could be found in the vagina of normal women during pregnancy, an endogenous theory of origin was proposed, in addition. Still later, largely as the result of Colebrook's work, it was found that some examples of the disease resulted from the transfer of streptococci from the throats of attendants, nurses and physicians, to the reproductive tract of the woman during labor and puerperium. The validity of this theory is attested to by the decrease in the morbidity in those clinics where there is an accurate control of the bacterial flora, particularly of streptococci, in the attendants. About 5 per cent of persons carry hemolytic streptococci in the secretions of the nose and

pharynx. In certain epidemics of puerperal infection due to the hemolytic streptococcus, streptococci have been found in as high as 25 per cent of the throats of attendants (Bryce and Tewsley). There is no evidence that the incidence of puerperal infection is related to the age, the parity, or the type of labor, although it is slightly more common in difficult labors than in normal spontaneous deliveries.

Clinicopathologic Correlation. The exudate within the uterine cavity and the necrosis of the endometrium lead to a hemorrhagic or putrid lochia. Thrombosis in the pelvic veins may lead to edema of the draining parts. The thrombosis occasionally extends into the femoral veins and produces the characteristic "milk leg." The bacteremia and pyemia are similar to that found in many infectious diseases.

Puerperal Infections Caused by *Clostridium Welchii*. A few puerperal infections, especially following induced abortion, are caused by *Clostridium welchii*. There is a severe, necrotizing or gangrenous inflammation of the uterus with the formation of gas in the wall of the uterus and in other tissues. The bacterium has a definite capsule and thereby differs from the clostridia in the vaginal canal, which are nonpathogenic (Butler).

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XXXII

Infections of the Oral Cavity

In addition to the lesions of the mouth which are a part of systemic disease in specific infections—tuberculosis, syphilis, leprosy, actinomycosis, foot-and-mouth disease, and thrush—there are additional bacterial and spirochetal diseases in which the portal of entry is the mouth, and the lesions are for the most part confined to the buccal cavity and adjacent tissues. The more important of these are oral fusospirochetosis, phlegmon of the floor of the mouth, noma, and secondary parotiditis.

brane. The tissue for several millimeters about the ulcer is elevated and dark purplish red. Similar lesions may occur on the tonsils or on the tonsillar pillars. Extensive ulceration with necrosis of the entire mouth gives the clinical picture of noma (Black).

Pulmonary Lesions. In the lungs and bronchi, usually following the administration of a general anesthetic or after operations on the upper respiratory tract, a peculiar type of gangrene may be observed. In one or more of the



Fig. 146. Oral fusospirochetosis (Vincent's angina). (Photograph by courtesy of Dr. Theo. Walsh.)

Oral Fusospirochetosis—Vincent's Angina (Trench Mouth)

Oral Lesions. The lesion in the mouth in Vincent's angina is essentially a gingivostomatitis. The gums are swollen, red, and spongy. Pressure on them causes an exudation of a thick, yellow, foul-smelling pus. At one or more points on the gingiva or on the buccal mucous membrane there are small or large, ragged ulcers, covered by a gray, thick mem-

lower lobes there are ragged, brownish green, foul-smelling cavities, varying from 1 to 10 cm. in diameter. Microscopic study of the wall of the cavity shows only necrosis with practically no infiltration of cells and no proliferation of the fixed tissue elements. In the necrotic tissue, either by smear or in sections, large numbers of spirochetes and fusiform bacilli may be seen. Cultures show, in addition, staphylococci and streptococci. In the bronchi the mucous membrane is swollen and

occasionally ulcerated, with a similar histologic picture to that in the pulmonary cavities. Study of a large series of cases indicates that the inflammation begins in the peribronchiolar tissues and spreads in both directions (Kline and Berger). By intratracheal inoculation of the pus it is possible to produce a similar condition in animals (Smith).

Causal Agent. The spirochete of Vincent is 12 to 14 microns in length and is readily seen in either darkfield or stained preparations. By observation of the type of motion and the morphology it can be differentiated from the other varieties of spirochetes found in the mouth—*Treponema microdentium*, *Treponema macrodentium*, and *Treponema buccale*. The fusiform bacillus is readily stained and has been cultured on special media under special conditions. It has been suggested that the two organisms represent different forms of the same species (Tunnickliff), but this cannot be regarded as proven.

Predisposing Factors. Spirochetes and fusiform bacilli may be found in the mouth of over 80 per cent of all adults, and it is evident that some other factor than the mere presence of the spirochete is necessary to initiate the disease. The organisms are also found in the smegma and in the vaginal secretions of a considerable percentage of persons. Their constant presence in certain lesions of the mouth, lung, and genital tract, however, and their ability to reproduce a similar condition in animals furnish evidence for their causal relation to disease. They are of extremely low virulence and invasive power, and before they can gain a foothold there must be some initial injury to the tissues, or mechanical trauma to the mucous membranes. This viewpoint is borne out by the observation that pellagrins with a Vincent's infection of the mouth are completely cured by the administration of nicotinic acid.

Noma

Noma or cancrum oris is an ulcerative, gangrenous stomatitis. It usually begins as a bluish red swelling of the mucous membrane of the cheek or of the corner of the lip. Intra-epithelial vesicles form. The inflammation progresses to involve the entire thickness of the cheek and there is ulceration of the mu-

cous membrane. The skin of the cheek is mummified and the entire mass becomes necrotic and sloughs out, leaving a large defect. For a distance of a few millimeters from the edge of the defect, the tissue is dark red and friable, but there is little infiltration of cells.

Noma is a disease of children, of debilitated persons, and of poorly nourished persons. It is frequently a late complication of other infectious diseases, such as kala-azar, measles, scarlet fever, malaria, and dysentery. Bacteriologic study reveals many organisms, but

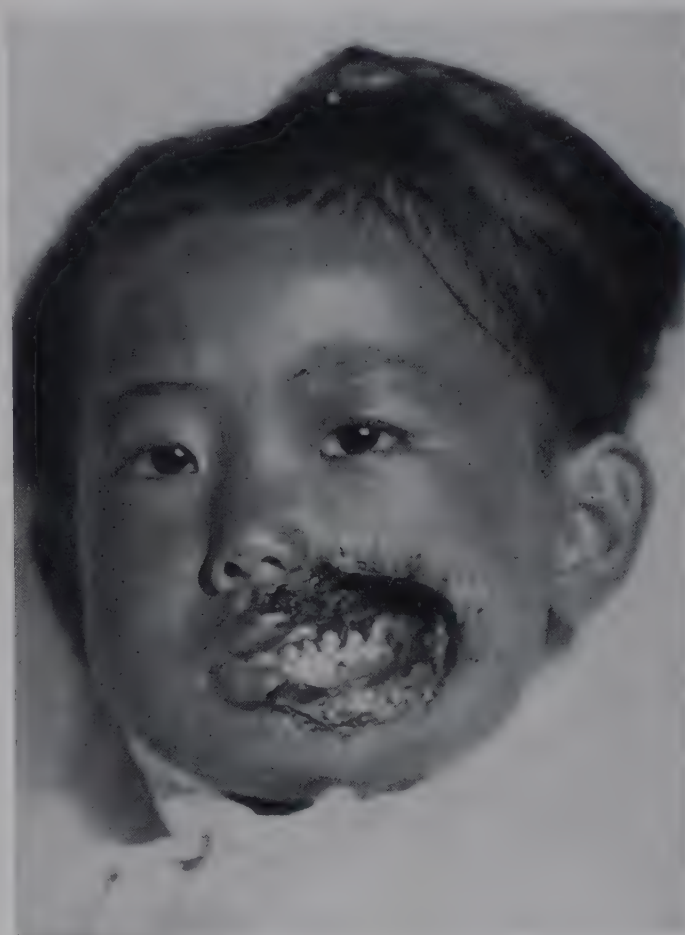


Fig 147. Noma in a child with kala-azar. (Photograph by courtesy of Prof. C. H. Hu.)

fusiform bacilli and spirochetes, anaerobic streptococci, and staphylococci predominate. The mortality varies directly with the severity of the associated illness, but it is always high (Burkwall).

Phlegmon of the Floor of the Mouth

Von Ludwig in 1936 described a condition in which there was profound necrotizing inflammation of the deep cellular tissues of the floor of the mouth and the neck. The inflammation begins in the region of the submaxillary salivary gland and contains numerous bacteria, predominantly the fusiform bacillus and spirochete and pyogenic cocci. In about

four-fifths of the cases the disease follows the extraction of a lower molar tooth. The gross and microscopic characteristics are essentially those of a necrotizing inflammation, and it is frequently spoken of as Ludwig's angina (Trout). A similar chronic cellulitis of the floor of the mouth and neck is designated as Holz phlegmon. There is little tendency to suppuration.

Secondary Parotiditis

In a few postoperative patients, and in debilitated persons, a suppurative inflammation of the parotid gland, usually caused by the staphylococcus, may develop. The parotid or at times the submaxillary and sublingual glands are swollen, soft, and red. The capsule is edematous, and on section a quantity of thick purulent fluid can be expressed from foci throughout the gland. Microscopically, typical abscess formation is seen with many polymorphonuclear leukocytes. These abscesses tend to originate in the larger ducts, indicating that the disease is basically an ascending ductal infection. The most important predisposing factor is probably dehydration and dryness of the mouth (Blair and Padgett). The inflammation in the gland is reflected clinically by redness, swelling, and pain over the angle of the jaw. Systemic symptoms are difficult to evaluate because most of the patients are desperately ill from some other condition. The usual mortality rate is about 50 per cent, but this has been considerably reduced by the use of radiant energy and antibiotics (Impink).

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XXXIII

Diseases Contracted by Ingestion of Contaminated Food and Drink: Food Poisoning

Ingestion of food contaminated by bacteria may give rise: (1) to disease caused by toxic substances formed by the bacteria outside the body—a toxic type, or (2) to disease caused by bacteria in the food which multiply inside the body—an infective type. The first will be considered in this chapter, and the second in the following chapter.

The best known examples of the toxic type are botulism and staphylococcal food poisoning.

Botulism

Pathologic Anatomy. Pathologic changes in botulism are largely those of hyperemia, hemorrhage, and thrombosis. The viscera and the brain are hyperemic, and throughout the parenchymatous organs and in the serous membranes there are numerous petechiae and ecchymoses, especially in the base of the brain and in the brain stem. Thrombi are found in all organs. They are adherent to the wall or free in the lumen, and consist of dense masses of fibrin, arranged in thick bands, with enmeshed polymorphonuclear leukocytes. In early stages only hyaline material or masses of loose fibrin are demonstrable. The thrombi are rarely seen before the third day of the disease. Changes in the motor ganglion cells of the brain and cord do not go beyond non-specific degeneration. Parenchymal cells in the liver, kidney, and myocardium may show cloudy swelling, fatty degeneration, or necrosis. If death is delayed, a bronchopneumonia is usual (Dickson).

Vehicles for Toxin. Botulism is an intoxication and not an infection. It is caused by ingestion of food that has been improperly smoked, pickled, or canned, allowed to stand for days or weeks, and eaten before cooking.

In Europe most cases have been caused by sausage (Latin, “botulus”: sausage) and preserved meats, while in America the food has generally been canned fruits and vegetables. Since 1897 there have been about 400 outbreaks in the United States.

Causal Agent. *Clostridium botulinum* is a normal inhabitant of the surface layer of the soil, from which it is transferred to food. When ingested it is unable to grow and establish an infection or an intoxication. In a suspected case, the following steps may prove useful in establishing a diagnosis: (1) demonstration of toxin in the suspected food, (2) isolation of *Clostridium botulinum* from the food, and (3) isolation of the *Clostridium* from the intestine or liver. The toxin is identified by injection into guinea pigs with and without simultaneous injection of specific antitoxin.

Clinicopathologic Correlation. The incubation period is usually less than twenty-four hours. The symptoms are largely those of motor paralysis, especially of the ocular, pharyngeal, and laryngeal muscles, probably the result of the action of the toxin on the peripheral nerve terminals. Antitoxin has not proved too effective in treatment. The mortality in America averages 60 per cent, and death occurs in some four to eight days from cardiac or respiratory failure. Antitoxin is present in the serum of recovered patients.

Botulism in Animals. Forage poisoning in horses and cattle and limberneck in chickens and ducks are examples of botulism.

Staphylococcal Food Poisoning

Some strains of the staphylococcus elaborate a soluble toxin which, if ingested, sets up within one to two hours a violent clinical

syndrome characterized by nausea, vomiting, abdominal pain, cramps, diarrhea, and weakness. The mortality is 5 to 10 per cent (Dack, Cary, Woolpert, and Wiggers). Pathologic changes are inconspicuous.

Most outbreaks follow the consumption of milk and milk products, such as cakes and eclairs filled with cream or custard. In a few, meat and fish have been incriminated. No one type of staphylococcus has been found, and the only known method to test toxin production is the feeding of a filtrate to human volunteers. Laboratory animals are not susceptible when fed the toxin, but succumb after intravenous injection. The nature of the toxin is unknown. It is only partly thermolabile. There is no immunity, although some persons develop an increased tolerance after repeated ingestion (Dack, Jordan, and Woolpert).

Other Types of Food Poisoning

From time to time, *Escherichia coli*, *Bacillus proteus* (Cooper, Davies, and Wiseman),

streptococci, and other bacteria have been isolated in pure culture from the food supposedly responsible for outbreaks of food poisoning. It must remain for future investigation to determine whether or not they are the cause.

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XXXIV

Diseases Contracted by Ingestion of Contaminated Food and Drink :
Enteric Infections

The enteric fevers and diarrheas were a plague to mankind, especially in wartime, until the twentieth century. Control of typhoid and dysentery in Europe and America is one of the great accomplishments of modern medicine. There are still regions of the earth where typhoid, dysentery, and cholera are widespread, and where little attempt has been made to insure a safe supply of water and milk for human consumption. Preventive medicine has much to do in this field.

Salmonellosis

As the knowledge of enteric infections has developed in the last century along the lines

vanced, it has become clear that any bacterium of the group may produce any type of disease. There is no longer merit in thinking clinically or pathologically of typhoid fever, paratyphoid fever, etc. These are etiologic entities only.

Types. Three major disease entities may be recognized: acute gastro-enteritis, typhoidal type disease, and localized lesions of organs other than the gastro-intestinal tract. The relative incidence of the bacterial type involved in human disease based on the studies of Seligmann, Saphra, and Wassermann is given in the table below. *Salmonella typhosa*, not included here, usually causes the typhoidal type of disease.

RELATION OF SALMONELLA TYPE TO TYPE OF DISEASE IN MAN

	Total Cases	Cases Showing		
		Gastroenteritis	Typhoidal Type	Localized Lesions
paratyphi	7	0	7	0
schottmülleri	63	20	39	4
typhimurium	312	284	12	16
cholerae-suis	78	16	38	24
oranienburg	50	40	5	5
newport	68	55	5	8
enteritidis	25	19	2	4
anatum	16	14	1	1

of bacteriology, pathology, clinical medicine, and public health control, there has been lack of correlation of knowledge. Hence pathologists and clinicians have come to recognize certain disease entities as associated with a specific causal agent. As information on the epidemiology and the bacteriology and immunology of enteric infections has been ad-

Pathologic Anatomy. *Gastroenteritis.* Both clinically and pathologically this type of the disease varies from a mild gastroenteritis to a fulminant inflammation, of the form seen in cholera.

The mucosa of the entire gastro-intestinal tract, especially the lower ileum and large intestine, is swollen, red, and velvety. The

lymphoid follicles are prominent but not as in the typhoid type. The mucosa is infiltrated with various cells, largely mononuclear cells but leukocytes may be present. Ulceration is rare except for small superficial erosions. The mesenteric nodes are enlarged and show hyperplasia. The spleen and liver are enlarged and in severe cases may contain grossly or microscopically demonstrable focal necroses.

Typhoidal Type. The most prominent pathologic changes are in the small intestine, the mesenteric lymph nodes, the liver, and spleen. The essential lesion in all is a proliferation of endothelial cells which are characterized by marked phagocytic activity. The character of the lesions in the intestine depends on the duration of the disease.

During the first week, the lymphoid tissue of both the solitary and conglomerate follicles

and filled with mononuclear cells. The blood vessels are dilated.

At the beginning of the second week, small foci of coagulation necrosis appear in the superficial parts of the hyperplastic lymphoid tissue. About the middle of the second week the necrotic tissue sloughs out and an ulcer is formed. In mild infections, the ulcers involve only a part of Peyer's patches, while in severe cases, the necrosis may extend through the entire wall and perforate the intestine. The first evidence of necrosis is a degeneration of mononuclear cells within the wall or lumen of a small lymphatic or vein. This is quickly followed by a deposition of fibrin and rapidly progresses to occlusion of the vessel and consequent necrosis of the region drained by the vessel. About the focus of necrosis leukocytes may accumulate.

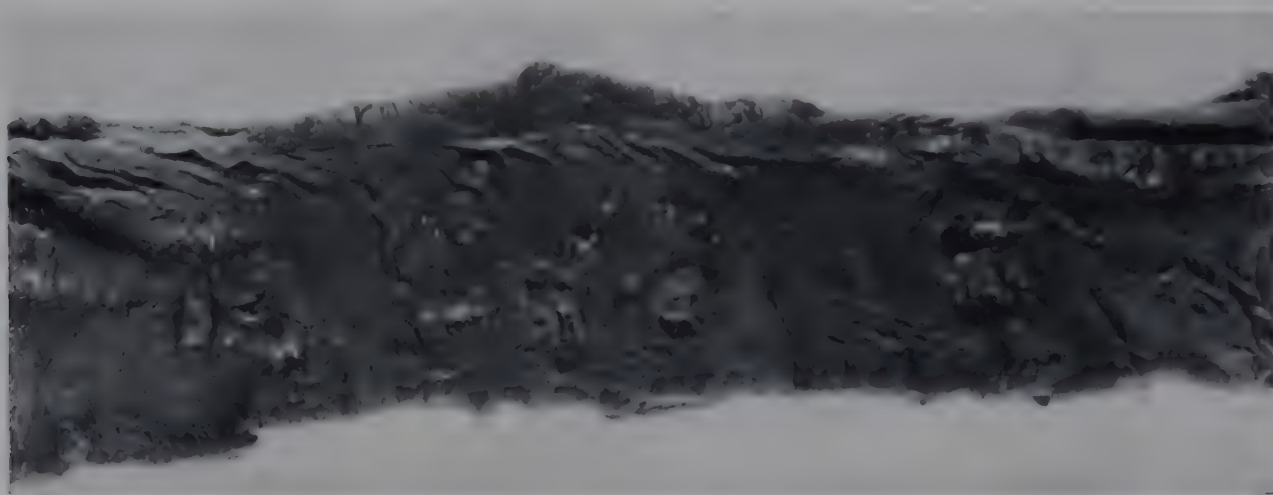


Fig. 148. Ulceration of small intestine in typhoid fever.

swells and forms sharply outlined, slightly overhanging masses projecting into the lumen. The increase in size is caused almost entirely by proliferation of the endothelial and reticular cells of the lymphoid tissue and by increase in the size of these cells. The typical cell is large—25 to 30 microns in diameter—oval or round, and has a vesicular nucleus and abundant cytoplasm. A few are multinucleated. Within the cytoplasm are many phagocytized lymphocytes and fewer red blood cells and leukocytes. In the surrounding lymphoid tissue, there are numerous cells in mitosis. In the mucosa adjacent to the follicles, there are edema, hyperemia, and numerous epithelial cells in karyokinesis, especially in the crypts of Lieberkühn. Changes in the muscularis and serosa are limited to slight infiltration with mononuclear cells in regions over Peyer's patches. The lymphatics of the wall are dilated

By the beginning of the third week, the height of the inflammatory process has been reached. The ulcer is oval, sharply punched out, and slightly undermined. The base is smooth. Toward the end of the third week, healing begins, granulation tissue fills the defect, epithelium covers the surface, and the lymphoid tissue reaccumulates. If the ulcer has extended into the muscularis, a scar forms.

The nature and progression of change in the mesenteric lymph nodes are identical with those in the intestine. The nodes are enlarged to three or four times normal size. The substance bulges from beneath the cut capsule and the tissue is soft and finely granular. There may be small foci of grayish yellow necrosis. Resolution is by fatty degeneration and autolysis of the hyperplastic cells.

The spleen is enlarged and weighs 300 to 600 gm. The pulp is typically soft or diffuent

and grayish red. Small foci of necrosis may be discernible grossly. The reticular cells of the malpighian bodies are hyperplastic and oc-

but the characteristic change is focal necrosis. During the first two weeks, large mononuclear cells accumulate diffusely and focally in the

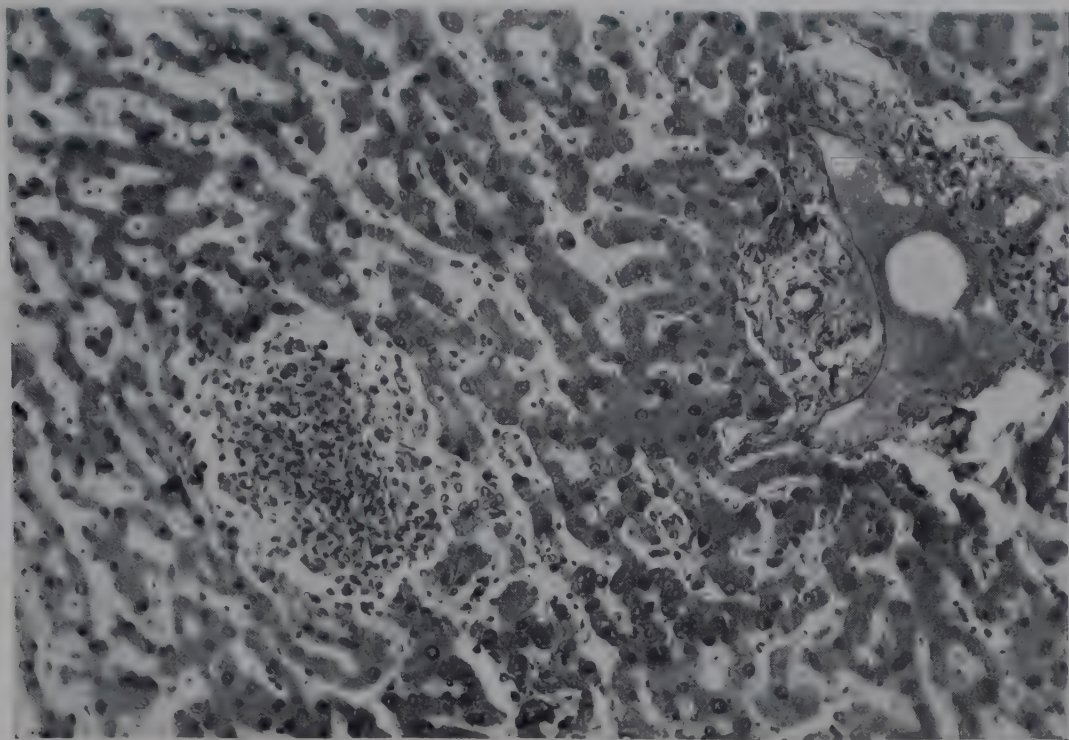


Fig. 149. Focal necrosis in liver in typhoid fever.

asionally necrotic. Throughout the sinuses are numerous mononuclear cells with phagocytized lymphocytes and red blood cells.

sinusoids. They increase by mitotic division until the hepatic cells are completely surrounded and the sinusoids are effectively

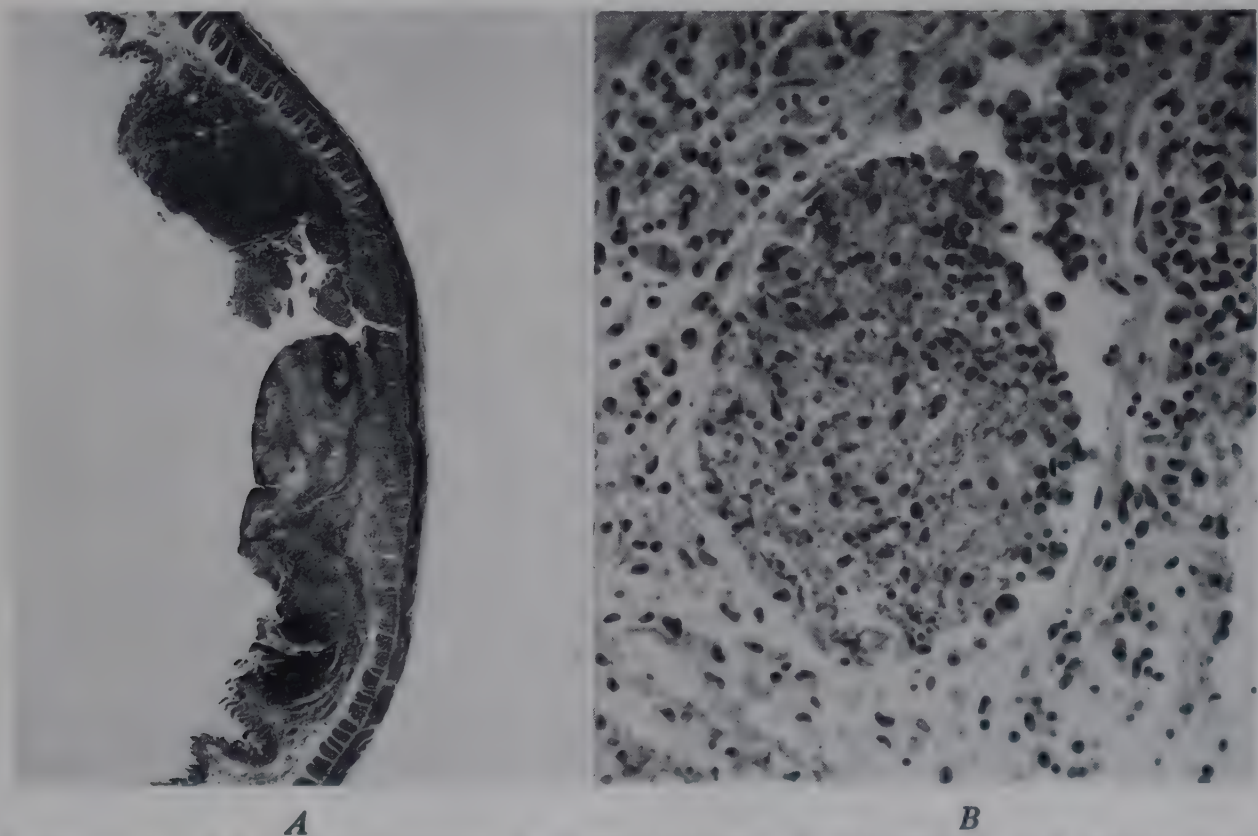


Fig. 150. *A*, Necrosis of lymphoid follicle in typhoid fever. *B*, Thrombus and cellular infiltration in a small lymphatic in typhoid fever.

The liver is slightly enlarged, soft, and yellow. Infiltration of portal spaces by lymphocytes, plasma cells, and mononuclear cells, and central necrosis are seen microscopically,

blocked in a focal region. At the beginning of the third week, the surrounded hepatic cells undergo necrosis to form the typical lesion (Mallory).

The heart is usually dilated, and the muscle is pale and flabby. The cross-striations of some fibers are indistinct, and the interstitial tissue is edematous. The skeletal muscle may be pale and shows Zenker's hyaline necrosis. The kidneys are slightly enlarged and are pale and flabby. The tubular epithelium shows degenerative changes, and some of the small vessels are filled with mononuclear cells. An acute cholecystitis is a not uncommon complication. In the respiratory tract, ulceration about the posterior commissure of the larynx occurs in about one-fourth of the cases, and in over one-half there is a pneumonia caused by the streptococcus or pneumococcus.

Localized Lesions. Lesions of organs other than the gastro-intestinal tract caused by bac-

with the region of the world, the age of the patient, and other factors. The figures of Felsenfeld and Young in Table 19, based on 6802 isolations in the midwestern United States, the southern United States, the Caribbean islands, and northern South America, are probably representative.

On the basis of animal sources, Edwards and Bruner report the dominant isolations from fowls of typhimurium and pullorum; from horses of typhimurium and abortus-equi; from swine of cholerae-suis; from carnivores of dublin and cholerae-suis; and from rodents of schottmülleri and enteritidis.

Mortality. The mortality in salmonellosis varies with the age of the patient, the type of disease, the invading organism, and other

TABLE 19. INCIDENCE OF SALMONELLA TYPES

Type	Per cent		
	Midwest	South	Caribbean
typhimurium	28.9	29.2	22.9
typhosa	8.4	7.1	15.2
montevideo	10.0	4.4	3.6
schottmülleri	7.4	7.1	4.6
oranienberg	6.3	3.6	6.1
derby	4.7	5.3	4.1
panama	4.7		5.6
anatum	2.6		7.6
all others	27.0	34.4	30.3

teria of the genus Salmonella include parotiditis, orchitis, endocarditis (Goulder, King-land, and Janeway), pericarditis, meningitis (Neal), arthritis, osteomyelitis, pneumonia, and abscesses of various organs.

The pathologic changes are essentially those of a cellular or suppurative inflammation, frequently with the mononuclear cell as the dominant cell type. There are no characteristic histologic features and the diagnosis must be established bacteriologically.

Causal Agent. On the basis of the bacterial content of both somatic (O) and flagellar (H) antigens, Bergey's Manual recognizes 151 types of Salmonella divided into 9 groups. In any suspected case of salmonellosis cultures should be made and the organism identified by biochemical reactions and antigenic content.

Incidence. The relative incidence of the various species and varieties of the genus Salmonella as a cause of human disease varies

factors. In general, a poor prognosis is related to occurrence in the young and old, to localization in organs other than the intestine such as heart and brain, and to infections with cholerae-suis, typhimurium, schottmülleri, oranienburg, and enteritidis (Seligmann, Saphra, and Wassermann).

Transmission. Salmonellosis is acquired by ingestion of contaminated food and drink or by handling of contaminated material. The source varies with the strain involved, with the region of the world, and other factors. In 1121 cases with a known source, Felsenfeld and Young list human carriers in 31 per cent, fowl eggs in 26 per cent, water in 24 per cent, fowl meat in 12 per cent, rodents in 3 per cent, pork in 3 per cent, and a human case in 1 per cent.

Carriers. About 10 per cent of all cultures of salmonella are isolated from persons without signs or symptoms of disease. Some of

these individuals have recovered from the disease and continue as carriers, others have never had the disease but become carriers, and still others are transient carriers because of recent ingestion of contaminated material.

Clinicopathologic Correlation. *Gastroenteritis.* The inflammation of the intestine leads to hypermotility and diarrhea. The loss of fluid and salts may result in dehydration and acidosis. In at least some instances there is an added element of food poisoning, since filtrates of some cultures induce hyperperistalsis in rabbits (Ecker and Biskind).

Typhoidal Type. The incubation period varies from five to fifteen days, and the course extends over four to five weeks. The average mortality rate was 10 per cent, before the introduction of chloromycetin. Severe infection

end of the second week, when ulceration is most active. Peritonitis may follow perforation of the intestine or gallbladder, or rupture of necrotic lymph nodes.

Bacillary Dysentery

The word dysentery (Greek, "bowel trouble") designates a clinical condition characterized by the frequent passage of stools containing blood and mucus, accompanied by straining and tenesmus. There are two major types: amebic, caused by the protozoon *Entamoeba histolytica*; and bacillary, caused by the bacterium *Shigella dysenteriae*. Occasionally a similar picture may be produced by other bacteria, such as *Streptococcus haemolyticus*, *Proteus*, and *Pseudomonas aeruginosa*;

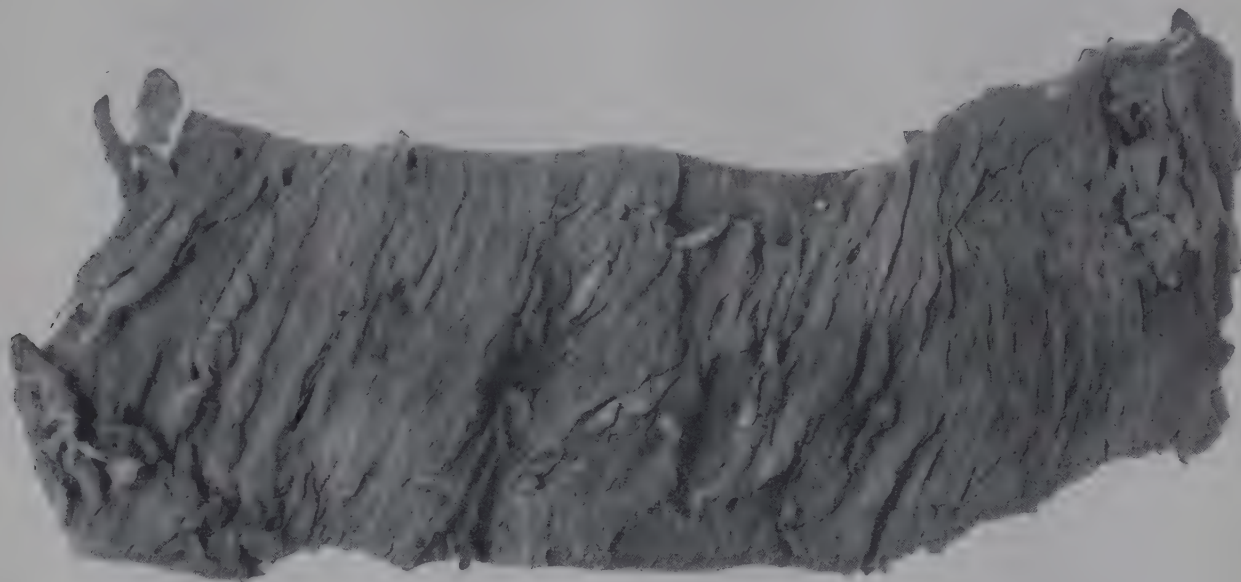


Fig. 151. Large intestine in bacillary dysentery.

is responsible for one-half of the deaths, and rarer complications for the remainder. True relapses occur in 10 per cent of patients, especially after early antibiotic therapy, with a mortality of 5 per cent.

The clinical signs and symptoms are characteristic and show the progression of changes. The infection throughout the course is responsible for the fever, weakness, and anorexia. Damage to the myocardium is probably the basis for the relative bradycardia and low blood pressure. The inflammation of the intestinal wall leads to diarrhea, and the resulting fluid and gas in the cecum and ascending colon give rise to the tenderness and gurgling in the right lower quadrant. The enlarged liver and spleen are usually palpable. The increased metabolism is associated with emaciation in the absence of an adequate caloric diet. Intestinal hemorrhage is most common at the

and by various other protozoa and metazoa, such as *Balantidium coli* and the hookworm. Many cases of bacillary dysentery in temperate climates may escape diagnosis under the titles of "summer complaint," "diarrhea" and "intestinal intoxication." The term "diarrhea" (Greek, "to flow through") should be reserved to designate the symptom of profuse watery stool, with or without blood and mucus. Many patients have both dysentery and diarrhea and there are intermediate stages between the two.

Pathologic Anatomy. In general the sigmoid and rectum are most frequently and severely affected, but lesions may be found in any part of the ileum and colon. The appendix is not infrequently involved. In many instances there is more advanced involvement in one area than in another, giving the appearance of a segmental type of enterocolitis. Rarely

there are lesions in the jejunum. In general the Shiga strain of the bacillus produces more acute necrotizing lesions than do the other strains.

In the acute stage there are edema and hyperemia of the mucosa, which is covered by a fibrinous or hemorrhagic exudate. Polymorphonuclear leukocytes are numerous in the tissues and in the exudate. There are many mitotic figures in the epithelial cells of the glands. The submucosa is greatly thickened by edema and hyperemia. The cells of the muscularis are swollen. In the submucosa, the

abscess. Over 50 per cent of cases develop a terminal discrete or confluent bronchopneumonia.

The liver may be the seat of cloudy swelling and fatty degeneration. In the kidney there is a distinct nephrosis. The epithelial cells are flattened, with dilated lumens filled with albuminous precipitate. In severe infections the ganglion cells of the brain and cord are swollen, and there is dissolution of the Nissl substance. There are numerous petechiae in the gray matter. The mesenteric lymph nodes are swollen and hyperemic, and microscop-

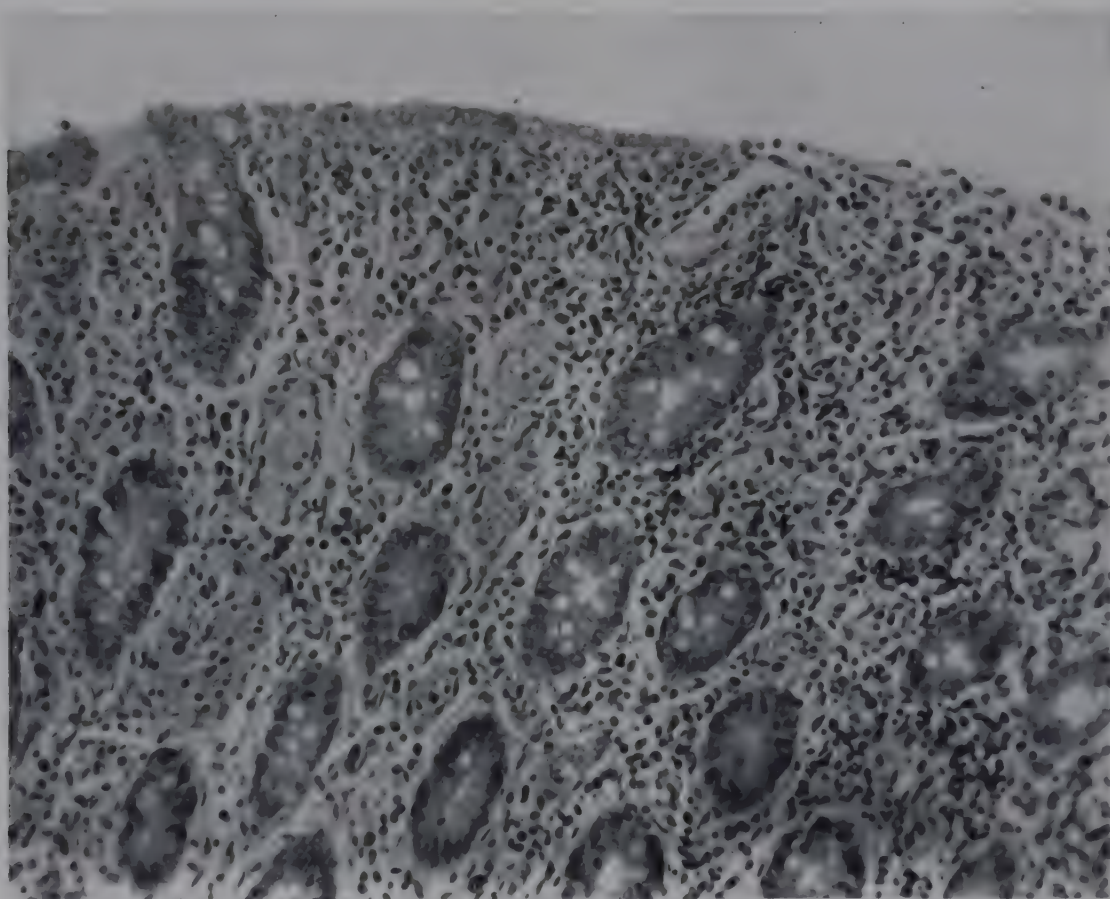


Fig. 152. Early stage of dysentery with inflammation of the mucosa.

mucosa, and the serosa there is slight to moderate infiltration with polymorphonuclear leukocytes, and the interstitial spaces are filled with a fibrinous exudate. The ulcers usually extend only to the muscularis mucosa, and the edges are necrotic or are covered by a serofibrinous exudate.

The chronic ulcers extend through the muscularis mucosa, and the base is usually formed by granulation tissue in the submucosa. They may burrow laterally and form an undermined edge. In an occasional case of chronic dysentery there is no ulceration. The predominant cells infiltrated into the tissues in the chronic stage are the lymphocyte, plasma cells, and mononuclear cell.

Rare complications in the intestine are perforation, stricture, pylephlebitis, and hepatic

ically hyperplasia of the reticulo-endothelial cells and active phagocytosis of leukocytes, lymphocytes, and red blood cells are seen. The spleen shows similar microscopic changes, and at times necrosis of the centers of the follicles. Lesions of the myocardium and arthritis are rare complications. Microscopic evidences of avitaminosis A are common: metaplasia of the epithelium in the trachea, bronchi, pancreas, bladder, and prostate. It is probable, however, that the low economic status and insufficient diet of the typical patient with dysentery are more important in accounting for these lesions than is the dysentery (Ch'in and Hu; Macumber).

Causal Agent. The pathologic picture of bacillary dysentery as described is caused by several varieties of bacillus, indistinguishable

on anatomic grounds. Cultures of the contents of the colon should be made on some differential plate medium, and suspicious colonies transferred to Russell's double sugar medium. Final identification is based on biologic reactions. The broad distinction is between mannite fermenters—Flexner, Sonne, Hiss-Russell, and Strong; and nonmannite fermenters—Shiga and Schmitz. The recently described Newcastle strain appears to be an antigenic subvariety of the Flexner strain (Boyd).

The Shiga strain differs from all the others in forming a heat-labile exotoxin when grown in a liquid medium. A heat-stable endotoxin may be demonstrated in all strains. Antibodies in the serum of ill patients include, in addition to antitoxins against both the exotoxin and endotoxin, bactericidal substances and agglutinins, and appear after the sixth day of the disease. A normal serum never agglutinates *Shigella dysenteriae* in dilutions above 1 to 20. Antitoxins are of value in the treatment of the disease, especially in the Shiga type. Final identification of all dysentery bacilli should be carried out by agglutination against known sera and by agglutination against the serum of the patient. This is especially important because closely related bacteria, such as *Shigella alkalescens*, are probably nonpathogenic and no antibodies are developed against them. Bacteria are only rarely present in the blood, the urine, and in tissues other than the intestinal wall.

Pathogenesis. The organisms enter the gastro-intestinal tract with contaminated food and water. If the gastric juice has an acidity lower than pH 5.5 the dysentery bacillus is destroyed (Felsen and Osofsky). In the colon they proliferate at a rapid rate and liberate the exotoxin. Many bacteria undergo autolysis and liberate the endotoxin (Penner and Bernheim). The latter is extremely toxic to the colon and produces edema, hemorrhage, and ulceration. The exotoxin is absorbed and acts on the central nervous system. The extensive ulceration in the chronic stage is probably the result of secondary bacterial infection with streptococci and other organisms.

Incidence. About 10,000 cases of bacillary dysentery are reported in the registration area of the continental United States each year. In general the Shiga strain is responsible for most of the epidemics in the Orient, while the Flexner strain is responsible for most sporadic

and endemic bacillary dysentery throughout the United States. Most examples of the disease in children are caused by the Flexner strain (Davison). The disease is more common in children than in adults, in men than in women, and in summer and fall than in winter and spring. Most of the cases in winter are caused by the Flexner strain, while many cases in the summer result from infection with the Shiga strain. Epidemics occur in asylums, prisons, hospitals (among the employees and intern staff), and in army camps. The outbreaks are definitely associated with crowded conditions and with some break in sanitation.

Transmission. Dysentery is transmitted by the same agencies which play a role in other intestinal diseases: water, food, flies, and the human carrier. A considerable percentage of persons who come in contact with a patient with bacillary dysentery harbor the organism in their intestines for a variable period of time without signs or symptoms of the disease (Watt, Hardy and De Capito). Epidemics, so characteristic of crowded groups, are initiated through the ingestion of food or water contaminated by a human carrier. During an epidemic there is direct transmission from man to man.

There is no known animal reservoir, and animals do not develop the disease spontaneously.

Relation to Regional Ileitis and Chronic Ulcerative Colitis. It has been suggested that these two characteristic diseases are caused by the dysentery bacillus because of their relation to epidemics of dysentery, demonstration of bacilli and antibodies against the dysentery bacillus in patients, and the similarity of pathologic changes in a small percentage of cases. At the present time this relation is unproven (Felsen).

Infection with *Shigella Dysenteriae* without Intestinal Lesions. In an extremely rare instance, a debilitated and undernourished child may develop meningitis caused by *Shigella dysenteriae* without demonstrable lesions of the intestine (Ch'in and Hu).

Clinicopathologic Correlation. The incubation period may be as short as twelve hours, and averages one to five days. The mortality varies from 6 to 20 per cent in the endemic form and may be as high as 30 per cent during an epidemic, especially with the Shiga strain. The inflammation of the intestine leads to

hyperperistalsis, with abdominal cramps and diarrhea, and may produce tenderness over the abdomen. The inflammation is usually of a hemorrhagic and catarrhal type, so that the stools contain quantities of blood and mucus. Absorption of the exotoxin of the Shiga strain is responsible for the neurologic signs of paralysis and polyneuritis. It is possible that the meningitic type of the disease is associated with excessive amounts of exotoxin (Felsen). There is usually a slight leukocytosis, and in an occasional patient there are depressions of the bone marrow and a severe progressive neutropenia. Anatomic changes in the kidney—nephrosis—result in oliguria and albuminuria with casts. The usual course is one to two weeks, after which there is recovery, transition to a chronic disease lasting for months or years, or death. In the chronic form the continued loss of blood through the ulcerations in the colon may lead to moderate to severe anemia.

Cholera

Pathologic Anatomy. In fatal cases of cholera there is extreme dehydration and emaciation. Extreme rigor mortis appears early. The face is shrunken, the eyes are sunken, and the skin is wrinkled and dry. All of the tissues, especially the subcutaneous tissues, the muscles, and the peritoneum, are dry and sticky. The small intestine is dilated. The lumen is overdistended with fluid contents—the “rice-water stools” of cholera. The lymphoid follicles of the ileum are prominent, the mucosa is hyperemic and edematous, and the epithelium is denuded. Vibrios are easily demonstrated in the superficial layers of the mucosa, in or just beneath the epithelial cells of the crypts. The other viscera, especially the kidneys, are hyperemic and may show cloudy swelling or fatty degeneration (Chatterjee). The spleen is characteristically small. In patients living over five to seven days, a bronchopneumonia from which cholera vibrios can be isolated is not uncommon.

Pathogenesis. The ingested cholera vibrios which escape the lethal effect of the gastric juices proliferate in the lumen and mucosa of the intestine. As some organisms die they undergo lysis and liberate a powerful endotoxin that is probably responsible for many of the gastro-intestinal disturbances. First water and then salts pass from the blood into the

lumen of the intestine, so that the specific gravity of the blood may be increased to 1.078 and the red blood cell count may reach 8,000,000.

Causal Agent. *Vibrio cholerae* is a small, comma-shaped rod that grows easily on ordinary culture media under aerobic conditions. It is present in the intestinal lumen, but has only rarely been recovered from the blood and other viscera. The isolated vibrio may be positively identified by agglutination with known serum, with attention to both the H and the O antigen; and by lysis when injected with immune serum into the peritoneal cavity of the guinea pig—Pfeiffer phenomenon (Linton).

Transmission. Infections are acquired by ingestion of food or drink containing the vibrios derived either from actively diseased persons or carriers. As many as 6 to 7 per cent of healthy persons living in endemic regions may be carriers. Specifically, infections may be acquired from consumption of water admixed with sewage, from clothes washed in sewage-polluted streams, from fresh vegetables fertilized with human excreta, from prepared food contaminated by flies, and from the fomites of patients.

Geographic Distribution. In the last decade cholera has been endemic in most of India, Afghanistan, and parts of China. In India there are an average of 200,000 deaths from cholera each year. Isolated epidemics have been reported in Iraq, Manchuria, Japan, the Celebes, and the Malay States. Cholera has never been a problem in Australia, New Zealand, the west coast, interior, and south end of Africa, in the isolated islands of the Pacific, or in the northern part of Europe, Asia, and America. There has been no case of cholera in the interior of the United States since 1911.

Clinicopathologic Correlation. The incubation period is rarely over forty-eight hours. Most of the signs and symptoms are related to the loss of water and salt in the stool and in the vomitus, and consequent extreme dehydration and hemoconcentration. The more notable of these are cramps in the legs and arms, prostration, thirst, oliguria or anuria, rapid and weak cardiac action, fall of blood pressure, and shallow and rapid respirations. The average mortality is 50 per cent. Two-thirds of the deaths result from collapse and one-

third from uremia. Prevention of the disease depends on adequate sanitary control of the food and water supply, isolation of active cases, and eradication of carriers. Prophylactic vaccination seems to confer some immunity for three to six months.

Brucellosis

The disease now known as brucellosis or undulant fever first attracted attention and was studied intensively during the Crimean War,

liver, kidney, lymph nodes and bone marrow. Less common lesions are a vegetative endocarditis (Levy and Singerman), a nodular type of bronchopneumonia, a chronic osteomyelitis, a meningo-encephalitis (Hansman and Schenken), and an oophoritis, salpingitis, epididymitis, or orchitis (Sharp). Necrosis, fibrosis, and calcification have been observed in the placenta (Harris). The dermal lesions have not been adequately studied.

Causal Agent. The three species, *Brucella melitensis*, *Brucella abortus*, and *Brucella suis*,

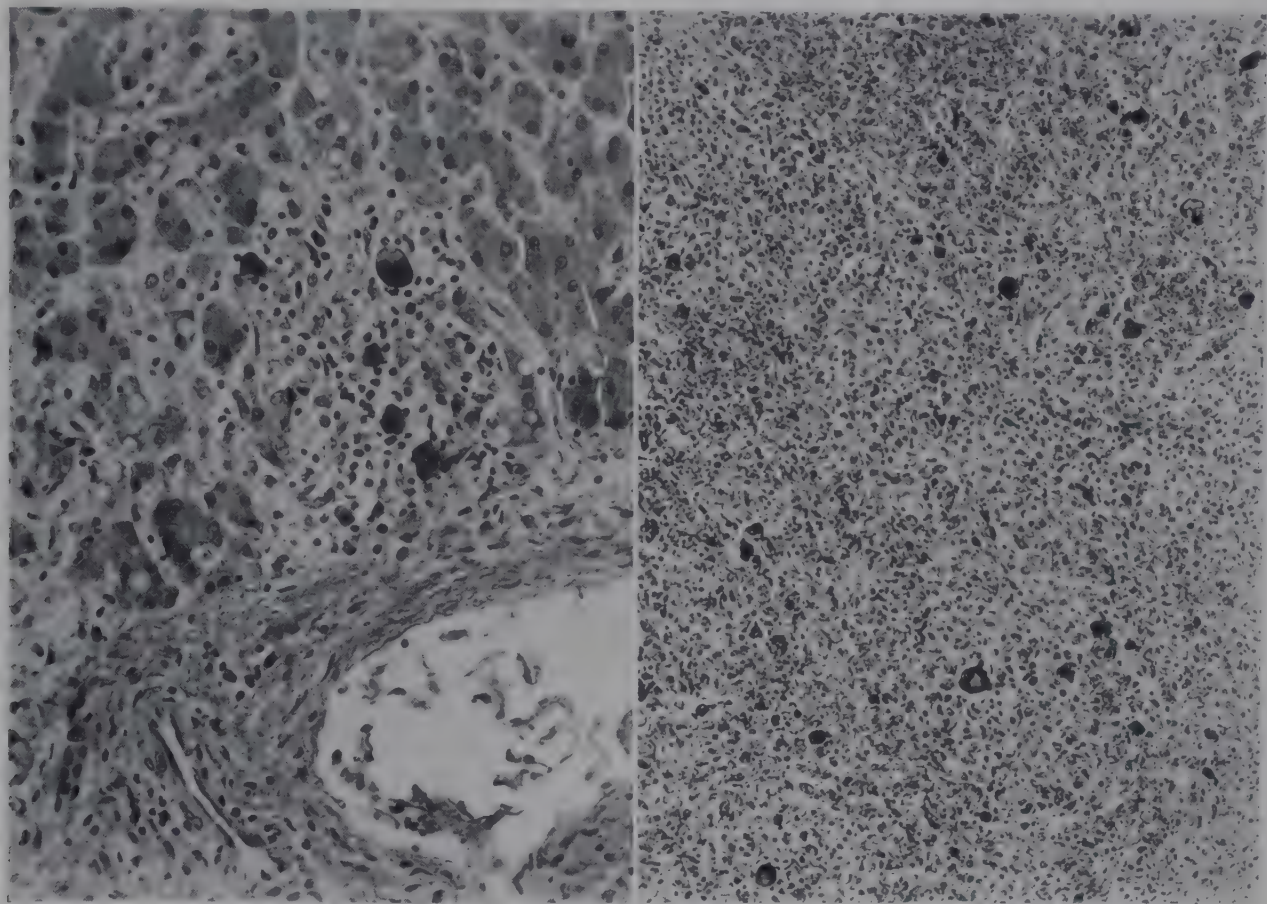


Fig. 153. Granulomatous lesions in the spleen and liver in brucellosis. (Armed Forces Institute of Pathology, Neg. Nos. 76673 and 76672.)

when large numbers of British troops were quartered on the island of Malta in the Mediterranean. Sir David Bruce isolated the bacterium in 1886. The first recognized case in the United States was reported by Craig in 1905.

Pathologic Anatomy. The pathologic changes of brucellosis are essentially those of a granulomatous disease. In the liver, spleen, lymph nodes, and bone marrow there are small granulomas consisting of cellular infiltration of lymphocytes within some giant cells and epithelioid cells (Spink, Hall, and Brande).

In fatal cases hyperplasia of Peyer's patches, with ulceration and hemorrhage, may be a prominent feature (Sprunt and McBryde). Chronic abscesses occasionally form in the

all pathogenic for man, can be grown from the blood and tissues only under special cultural conditions (Poston). Antibodies formed may be identified by an agglutination test, a skin test of hypersensitivity, and an opsonocytaphagic test. The diagnostic value of all of these has been questioned.

Incidence. Human brucellosis has been reported from all parts of the world, but is most common in rural communities. The peak incidence is in adult life. It is claimed by some that 10 per cent of the people of the United States have been infected, and that 1 per cent of these are ill of the disease at any one time (Gould and Huddleson). Further studies will be necessary to establish the view that brucellosis is a common endemic disease in the United States.

Transmission. Brucellosis in most instances is transmitted to man by ingestion of milk and dairy products from infected cows and goats. Less common sources are contact with infected animals, handling of fresh meat from diseased animals, and exposure to cultures in the laboratory. About 10 per cent of all milk cows and 1 to 20 per cent of all hogs (varying with location) in the United States are infected. Adequate pasteurization or boiling of milk will prevent most human infections.

Clinicopathologic Correlation. The incubation period varies from five to thirty days. The most important symptoms are those of an acute or chronic systemic febrile illness: fever, chills, sweating, anoxia, headache, muscular pain, and weakness. There are few localizing signs except the enlargement of the liver, spleen, and lymph nodes (Spink, Hall, and Brande).

Abortion in Mammals. There is no question of the relation of brucella to abortion in cows and pigs, but its relation to abortion in woman has not been clearly established. In a few patients with repeated abortion, brucella has been cultured from the lochia and pathologic changes demonstrated in the placenta (Harris). The problem is worthy of more intensive study.

Relation to Hodgkin's Disease. Poston and her associates at Duke University have reported the isolation of brucella from the tissues and blood of patients with Hodgkin's disease. It must remain for further study to define the relation between the two.

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Miscellaneous Infections of the Gastro-intestinal Tract

In addition to the bacteria ordinarily recognized as intestinal bacteria, the pathogenic activity of which will be discussed in the following chapter, the lumen of the lower intestine from time to time contains other pathogenic bacilli and cocci. The most important from the standpoint of disease are the streptococci.

Phlegmonous Gastritis

Pathologic Anatomy. In phlegmonous gastritis the principal pathologic change is in the submucosa of the stomach, which is increased in thickness to as much as 1 or 2 cm. by a diffuse and a focal inflammatory reaction. Pus may be expressed from the cut section. The mucosa is thickened, edematous, and dark red or purple. The muscularis is only slightly thickened, and the peritoneum is edematous and hyperemic. There is tremendous edema and infiltration with polymorphonuclear leukocytes, especially in the submucosa. In focal regions there may be small or large abscesses, with complete necrosis of the involved tissues.

Bacterial Causes. About 70 per cent of cases of phlegmonous gastritis are due to the streptococcus. The organism may be brought to the stomach either through the lumen or by the blood stream. Rarely the organisms are introduced from without through a perforating wound of the abdomen or during a surgical operation. It is more common in men than in women and in the lower economic groups than in the well-to-do. A significant percentage of patients have a history of chronic alcoholism.

Enteritis and Enterocolitis

In addition to the specific diseases of the gastro-intestinal tract described in the pre-

ceding chapter, an inflammation of the wall of the intestine may be seen as a nonspecific primary or secondary disease.

Pathologic Anatomy. The mucous membrane of the ileum or colon or both is swollen and velvety. The lymphoid follicles, both solitary and conglomerate, are conspicuous, and in the center of many of the solitary follicles there is a small, superficial ulceration. The blood vessels of the wall and of the serosa are dilated. The lumen is filled with a liquid, fecal material, and the finding of this type of intestinal content in the colon beyond the hepatic flexure is the anatomic evidence of diarrhea. The changes in the wall as seen microscopically are frequently inconspicuous and not consistent with the intensity of the gross alterations. The capillaries and lymphatics of the mucosa are dilated, and the interstitial tissue is edematous and infiltrated with lymphocytes, plasma cells, polymorphonuclear leukocytes, and eosinophils. There are numerous mitotic figures in the cells of the deeper intestinal glands. The lymphoid follicles are hyperplastic. The smooth muscle fibers of the muscularis are vacuolated.

Intestinal Pneumatosis. In an occasional example of acute ulcerative enteritis, especially in children, there are numerous small bubbles of gas in the submucosa of the intestine—a condition known as “intestinal pneumatosis.” The gas has the same composition as that in the intestine, and it is assumed that the intestinal gas is driven into the wall through an ulcer (Judge, Cassidy, and Rice).

Epidemic Infectious Diarrhea of the New-born Infant. Hemolytic streptococci can be isolated from the stools and peritoneal exudate in nearly all cases of this disease. In fatal cases there is advanced emaciation and dehydration. The mucosa of the small and large intestine is swollen, red, and granular. There

is advanced infiltration with polymorphonuclear leukocytes and superficial ulceration. Bronchopneumonia is a frequent complication. The condition is more common in premature infants than in term infants (Cron, Shutter, and Lahmann). The mortality is high, and the epidemic is rarely checked until the hospital is closed and completely renovated.

Appendicitis

Pathologic Anatomy. The appearance of the appendix in acute appendicitis varies with

atous and hyperemic. The small veins and lymphatics of the meso-appendix are dilated and frequently filled with infected thrombi. The lymph nodes of the meso-appendix are hyperplastic (Fig. 154).

Complications. Aside from generalized peritonitis and pylephlebitis, which are discussed later in this chapter, the most important complication of acute appendicitis is periappendiceal abscess.

Periappendiceal Abscess. Early or late in the course of acute appendicitis a localized suppurative inflammation may develop in the

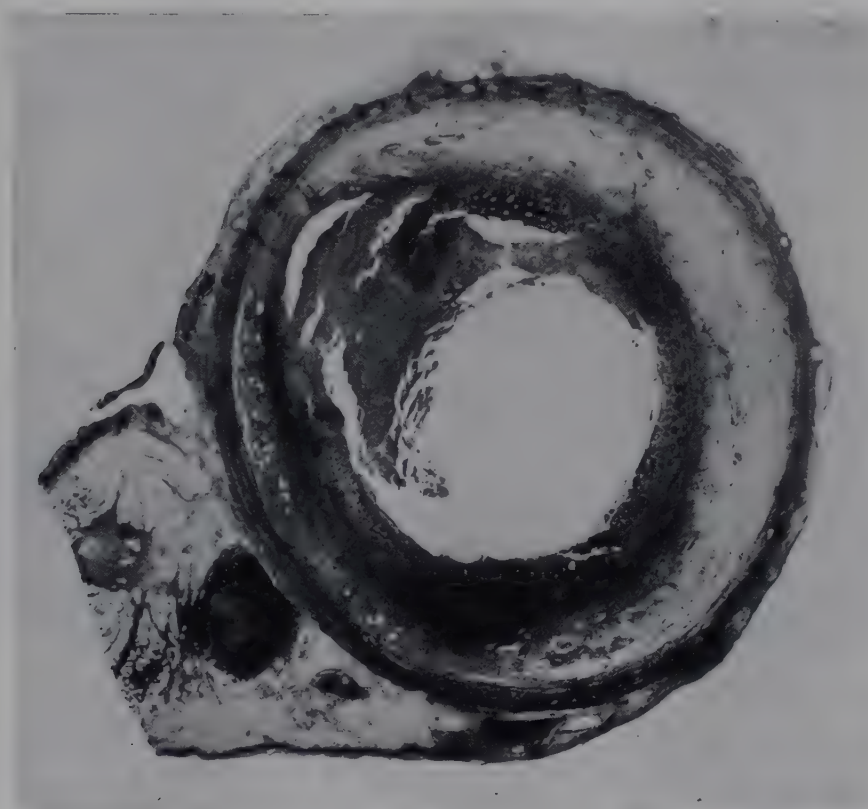


Fig. 154. Acute appendicitis. Note the destruction of a part of the mucosa, the edema of the submucosa, and the enlargement of the lymph node and thrombus in a vein in the mesoappendix.

the type of inflammation—catarrhal, purulent, hemorrhagic, or necrotizing. The pathologic changes also depend on the presence or absence of obstruction by a fecalith in the proximal part of the lumen.

The mucosa is edematous, hyperemic, infiltrated with many polymorphonuclear leukocytes, and in places necrotic. The submucosa and muscularis are edematous and infiltrated with polymorphonuclear leukocytes. The lymphoid follicles are hyperplastic and in part necrotic. The blood vessels of the serosa are dilated, and on the serous surface there may be a fine fibrinous exudate. Frequently a localized point in the wall is completely necrotic, and there is a fistulous tract between the lumen and the peritoneal cavity. The fibroadipose tissue of the meso-appendix is edem-

peritoneal cavity about or behind the cecum or about the ileocecal junction and coils of the terminal ileum. Uniloculated or multiloculated cavities filled with pus constitute a tender, palpable mass in the right lower quadrant of the abdomen. In general the systemic response in appendicitis is greater when abscess is present; that is, there is a higher temperature, greater toxemia, and an increased leukocytosis. In retrocecal abscesses the right ureter may be involved and a fistula established (Hicken and Carlquist).

Bacterial Causes. In general the bacterial species recovered are the same bacteria present in the intestinal lumen. The important aerobic species are *Escherichia coli*, *Streptococcus nonhaemolyticus*, diphtheroid bacilli, *Bacillus lactis aerogenes*, *Streptococcus vir-*

idans, and *Streptococcus haemolyticus*. The notable anaerobic species are *Bacillus melanogenicum*, *Streptococcus nonhaemolyticus*, and *Streptococcus haemolyticus* (Altemeier). The streptococci are probably the most significant.

Predisposing Factors and Pathogenesis. Since the bacteria which cause appendicitis are constantly present in the lumen, it must be assumed that there are other factors which change the resistance of the tissues and allow the bacteria to invade. The most important of these are: (1) interruption of the continuity of the mucosal surface, (2) obstruction of the lumen, and (3) disturbances in circulation. Foreign bodies such as vegetable seeds, parasites such as *Oxyuris vermicularis*, and impacted fecaliths may disrupt or penetrate the mucosa. Obstruction of the lumen is usually

whorls of nerve fibers entangled in the fibrous tissue. These are known as "neuromas of the appendix" (Parker and Corrigan). The mechanism of obliteration of the lumen is not known (Collins).

Mucocele of the Appendix. Following obstruction of the proximal part of the lumen, the distal segment becomes distended with the secretion of the mucosa. If infection does not supervene, or if inflammation heals, the lumen is gradually distended by clear mucus. The wall is atrophic. The condition is present in about 2 per cent of all persons. Rupture into the peritoneal cavity may result in pseudomyxoma peritonei (Grodinsky and Rubnitz).

Recurrent and Chronic Appendicitis. Of patients subjected to appendicectomy for acute appendicitis, 25 to 35 per cent give a history of previous attacks. In these appen-

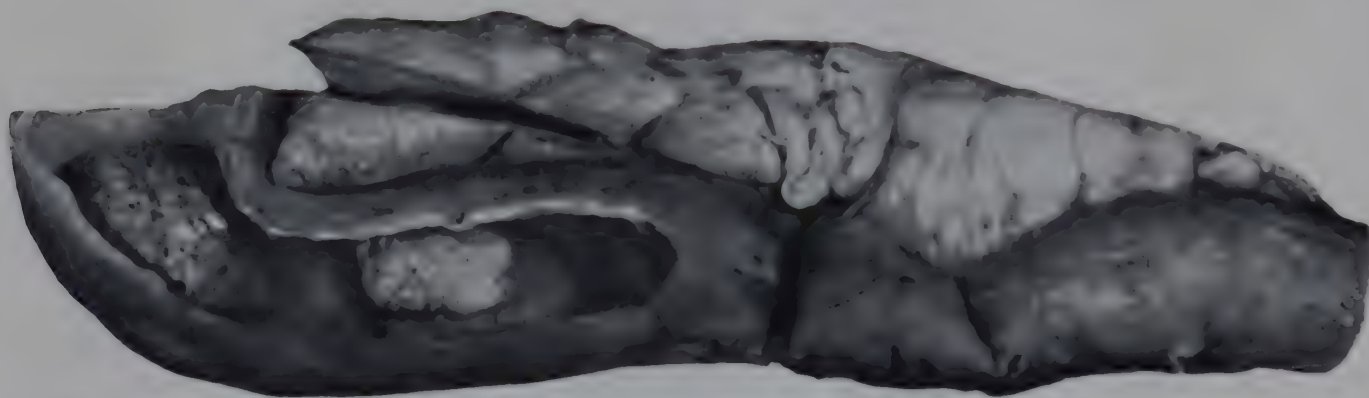


Fig. 155. Acute appendicitis with two fecaliths in the proximal part of the lumen.

caused by a fecalith, but a neuromuscular factor must also be considered. Fecaliths are present in about 60 per cent of all cases of acute appendicitis. The higher incidence of appendicitis in pregnancy is believed to be related to displacement and kinking of the appendix by the enlarging uterus (Baer, Reis, and Arens).

Fecaliths. Most true fecaliths are found in the appendix. They are concentrically laminated, spheroid bodies. One-half of the substance is soap, one-fourth inorganic salts, chiefly calcium phosphate, and one-fifth organic residue, mostly vegetable fibers (Maver and Wells). A seed, a foreign body, or a parasite is frequently the central nidus. They are present in 5 to 10 per cent of all appendices.

Obliteration of the Appendiceal Lumen. In a number of persons, increasing with age, the lumen of the appendix is partially or totally obliterated by fibro-adipose tissue infiltrated with lymphocytes, plasma cells, and mast cells (Collins). In a significant number there are

whorls of nerve fibers entangled in the fibrous tissue. These are known as "neuromas of the appendix" (Parker and Corrigan). The mechanism of obliteration of the lumen is not known (Collins).

Both the clinical picture and the pathologic anatomy of chronic appendicitis are yet to be delineated. It is the experience of those who have studied the results of appendicectomy for chronic appendicitis that only 1 per cent of patients are cured of the symptoms when there is not a history of one or more definite attacks of acute appendicitis (Alvarez). Many pathologic changes have been described, but significance cannot be attached to any of them with certainty.

Morbidity and Mortality. The highest incidence of acute appendicitis is in the third decade. The ratio of men to women is 6:4. The average mortality in American hospitals is 2 to 4 per cent. In uncomplicated acute appendicitis the mortality should be less than 1 per cent, while in appendicitis with perforation, about 7 per cent is to be expected. The percentage of deaths progressively increases

as the operative treatment is delayed. The mortality is highest in children and in the aged.

Clinicopathologic Correlation. The clinical signs and symptoms in appendicitis are the result of: (1) obstruction of the appendiceal lumen, and (2) the presence of inflammation. Obstruction of the lumen causes the sharp pain so characteristic of this phenomenon, whether it is in the intestine, in the ureter, or in the bile ducts. When inflammation involves the peritoneal surface, it leads to the more continuous dull type of pain. The nausea and vomiting are probably related to a disturbance in the neuromuscular mechanism of the small intestine, induced by inflammation in a nearby structure. The chills, fever, leukocytosis, and other manifestations of infection are not distinctive.

Peritonitis

Peritonitis is a contributory or primary cause in about 7 per cent of all deaths. The pathologic changes vary with the severity of the disease and the nature of the primary lesion.

Pathologic Anatomy. In the typical acute case of peritonitis the cavity contains 100 to 200 cc. of limpid, cloudy, or thick, purulent fluid. The peritoneal surfaces are dull and covered by a purulent or fibrous exudate. The subperitoneal blood vessels are dilated. The omentum may occupy the normal position, may be contracted to form a firm, hard mass just below the transverse colon, or may be directed to the point of origin of the peritonitis.

With subsidence of acute inflammation, there is beginning loculation of the exudate in from four to six days. The intestinal loops are adherent to one another by delicate fibrous adhesions, and when these are broken a quantity of pus is detected. After from five to eight days there is organization of the fibrinous loculation. Both the fibrinous and fibrous adhesions may kink the intestine and produce intestinal obstruction. In most types of peritonitis the small intestine is dilated—a finding consistent with the clinical observation of intestinal obstruction on the basis of paralysis of the musculature (paralytic ileus).

The pathologic changes in the other organs are those of infection.

Pathogenetic Types of Peritonitis. It is apparent that peritonitis cannot occur as a pri-

mary disease except after a penetrating wound of the abdominal wall. Secondary peritonitis follows a surgical operation with opening of the peritoneum in 22 per cent; acute appendicitis in 13 per cent; tuberculosis in 10 per cent; puerperal infection in 10 per cent; an associated malignant tumor in 5 per cent; perforation of a peptic ulcer in 5 per cent; and trauma in 4 per cent; and it is metastatic in 4 per cent (Pflaum). Other examples are related to diseases of the gallbladder, intestine, and mesentery.

Postoperative Peritonitis. The possible routes for entry of bacteria in postoperative peritonitis are: soiling of the peritoneum with intestinal content, rupture of the line of surgical sutures with leakage, and introduction of bacteria through the abdominal wound. That the first and second are the most important is shown by the fact that about one-half of all examples of postoperative peritonitis follow some surgical procedure involving opening of the gastro-intestinal tract.

VACCINATION OF THE PERITONEUM. EXPERIMENTAL PERITONITIS IN DOGS. Even with the best operative technique the peritoneum is occasionally soiled with feces containing the colon bacillus. Preoperative vaccination of the peritoneum (Steinberg) has been largely replaced by administration of sulfonamides.

Post-traumatic Peritonitis. Either penetrating or nonpenetrating injury to the abdominal wall may cause rupture of the intestine, bladder, or a solid viscus. The more common types of trauma are automobile accident, gunshot wounds, and stab wounds. Perforation of the intestine in the water-blast is a special type.

Metastatic Peritonitis. By the term "metastatic peritonitis" is meant those inflammations of the peritoneum which are not directly related to perforation or extensive disease of an abdominal viscus. Other terms used are "primary idiopathic peritonitis" and "migratory peritonitis." About two-thirds of the cases are caused by *Streptococcus haemolyticus* and about one-third by the pneumococcus. It is most frequently seen in children less than six years of age, and shows no preponderance in either sex except in the pneumococcal type without nephrosis, where there is a preponderance in girls. In most instances there is a history of a preceding otitis media (Ladd, Botsford, and Curnen).

PATHOGENESIS. There are four possible modes of entry for the bacteria: (1) through the blood stream, (2) through the vagina and fallopian tubes in girls, (3) through the wall of the gastro-intestinal tract, and (4) through the transdiaphragmatic lymphatics from associated pleurisy. Each of these is probably operative in different cases. Blood cultures are frequently positive, but this may represent invasion from the peritoneum rather than to it. Histologic studies of the intestinal wall show leukocytes in all layers, and the conclusion has

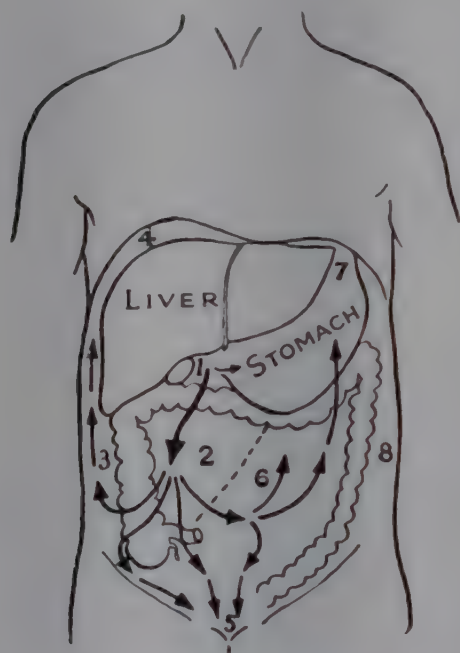


Fig. 156. Diagram of spreading peritonitis. The lines of spread suggested by Mitchell. The dotted line represents the attachment of the mesentery. 1, Exit from right subhepatic space, bounded by the inferior border of the quadrate lobe of the liver, the free edge of the falciform ligament, the fundus of the gallbladder, and the transverse colon. 2, Right infracolic space. 3, Right external paracolic groove. 4, Right subphrenic space. 5, Pelvic space. 6, Left infracolic space. 7, Left subphrenic space. 8, Left external paracolic groove. (Mitchell: Brit. J. Surg., Vol. 28.)

been drawn that this is migration through the wall from the lumen of the intestine (Wile and Saphir).

Bile Peritonitis. In association with many diseases of the gallbladder, bile ducts, and liver, inflammation of the peritoneum, associated with the presence of bile, is encountered. The source of the bile is frequently unknown. In the more careful investigations, actual perforation of the biliary system, perhaps microscopic, has been demonstrated. Since most diseases associated with perforation are also bacterial diseases, it is difficult to separate the effects of bile from those of the bacteria contained within the bile. In

experimental animals bile provokes a mild inflammation of the peritoneum, but the mortality in bile peritonitis averages 60 to 70 per cent in man. It therefore seems likely that the irritating influence of the biliary constituents is a minor factor. The signs and symptoms are essentially those of two conditions: first, the primary disease of the biliary system, and second, the peritonitis (McLaughlin).

Fetal Peritonitis. If the intestine of the fetus in utero is perforated, sterile meconium is extruded into the peritoneum, where through chemical irritation inflammation results. Similar changes follow perforation of the bladder with extravasation of the urine into the peritoneum. It is probable that some of the peritoneal adhesions and bands observed in children are the result of fetal peritonitis. Occasionally the perforation persists, and shortly after birth a virulent purulent peritonitis, caused by bacteria, appears (Abt).

Bacterial Causes. The bacterial causes of peritonitis are those of the primary disease, and therefore *Streptococcus haemolyticus* and *Escherichia coli* are the most common organisms.

Spread of Peritonitis. In most peritoneal infections the inflammation starts in a small focus, as about an acutely inflamed appendix, a perforating ulcer, or a leaking suture line in the intestine. The first line of defense is the omentum. It is drawn to the point of inflammation and may seal a hole in the intestine or effectively wall off an infection. The second line of defense, at times effective in confining inflammation to a part of the peritoneal cavity, is the intraperitoneal barriers or "watersheds." The longitudinal barrier consists of the vertebral column, the periaortic tissues, and the mesentery of the small intestine, and divides the cavity below the transverse colon into a right and left half. The transverse mesocolon and the pelvic brim divide the cavities into three transverse spaces: upper, middle, and lower. The upper transverse or supracolic space includes the right subphrenic space, the left subphrenic space, and the lesser peritoneal sac. The middle transverse space is divided by the longitudinal barrier into a right and left infracolic space. The lower transverse space is the pelvic cavity. The lines of spread from one of these spaces to another are shown in Fig. 156.

Subphrenic and Subhepatic Abscess. The

primary lesion of a subphrenic or subhepatic abscess is in 30 per cent acute appendicitis, in 28 per cent a perforating lesion of the stomach or duodenum, and in 12 per cent suppurative disease of the liver or bile ducts. There are four potential spaces: the right superior-anterior, the left inferior-anterior, the right inferior, and the left posterior-inferior. The right superior-anterior is involved in over half, and the others in 10 to 20 per cent each. In one-third there is extension to the pleura, either through the diaphragmatic lymphatics or by perforation of the diaphragm. The mortality in patients who have not been operated upon is 90 per cent, and in those with satisfactory surgical drainage is 33 per cent (Ochsner and DeBakey).

Clinicopathologic Correlation. The clinical signs and symptoms of acute peritonitis depend upon four anatomic and physiologic changes: (1) infection is responsible for the chills, fever, leukocytosis, and other well recognized symptoms; (2) stimulation of the nerve endings leads to pain, and this in turn to spasm of the muscles of the abdominal wall and rigidity; (3) a space-consuming exudate in the peritoneal cavity distends the abdomen; and (4) the motility of the intestine is inhibited by interference with the reflex pathways within the intestinal wall. With a block to the onward flow of fluid through the intestine, constipation and vomiting follow.

Fibrous Peritoneal Adhesions and Fibrous Thickening of the Peritoneum. On recovery from a fibrinous or purulent inflammation of the peritoneum, fibrous adhesions form. These may be the cause of either an acute or a chronic intestinal obstruction. Focal fibrous adhesions about the gallbladder and in the pelvis are related to diseases of those structures. In longstanding ascites, as in cirrhosis of the liver, there is slight diffuse or focal fibrous thickening of the peritoneum. Fibrous thickening of the peritoneum covering the liver and spleen and fibrous adhesions to surrounding structures are less easily explained. In some the thickening is extreme, and the connective tissue undergoes hyalinization to constitute the "Zuckerguss" type of capsule of the spleen or liver. In most there is no evident cause, but in a few there are associated fibrous adhesions in the pleura and pericardium—a condition known as "chronic polyserositis" or "Pick's disease."

Pylephlebitis

In infections of the drainage area of the portal vein the inflammation may be severe and may involve smaller venous radicles. An infected thrombus then forms and propagates in the lumen of the vein toward the liver. Small infected emboli break off and lodge in the intrahepatic branches of the portal vein, where they induce the formation of abscesses. The entire picture is known as "pylephlebitis" or "thrombophlebitis of the portal vein." It occurs most commonly after appendicitis, but may be a complication of chronic ulcerative colitis, diverticulitis, or of an infection from an ulcerated carcinoma of the colon (Thalhimer).

Pathologic Anatomy. The liver is enlarged, and throughout the parenchyma there are numerous small and large abscesses. The intrahepatic branches of the portal vein are filled with a soft, friable, yellow-gray thrombus, which in many places is liquefied to form pus. The hepatic parenchyma may show degenerative changes. The portal and superior mesenteric veins may or may not be filled with a soft thrombus, similar to that in the intrahepatic branches. Infected thrombi are readily demonstrated in the veins draining into the superior mesenteric vein. The inflammation in all tissues is characterized by necrosis and infiltration with polymorphonuclear leukocytes.

Bacterial Causes. Since acute appendicitis is the commonest associated lesion, and since appendicitis is most frequently caused by the streptococcus, it follows that most pylephlebitis is caused by the streptococcus. Occasional cases caused by Friedländer's bacillus, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Proteus vulgaris* have been observed.

Clinicopathologic Correlation. The signs and symptoms are largely those of the associated disease, plus the evidence of vascular invasion by bacteria—chill and fluctuating fever. The inflammation of the liver, particularly about the portal radicles, results in enlargement and interference with the excretion of bile, expressed clinically as pain in the abdomen and on palpation of the liver, and jaundice. The liver filters out most of the bacteria and a positive blood culture is unusual except terminally. Various statistics give the incidence of pylephlebitis as between 0.5 per

cent and 5 per cent of all patients with acute appendicitis. After the major branches of the superior mesenteric vein are involved, death in two to four weeks is the rule.

the appendix is normal but the mesenteric lymph nodes are enlarged, soft, and red. The usual term used is acute nonspecific lymphadenitis. Microscopic study shows hyperplasia

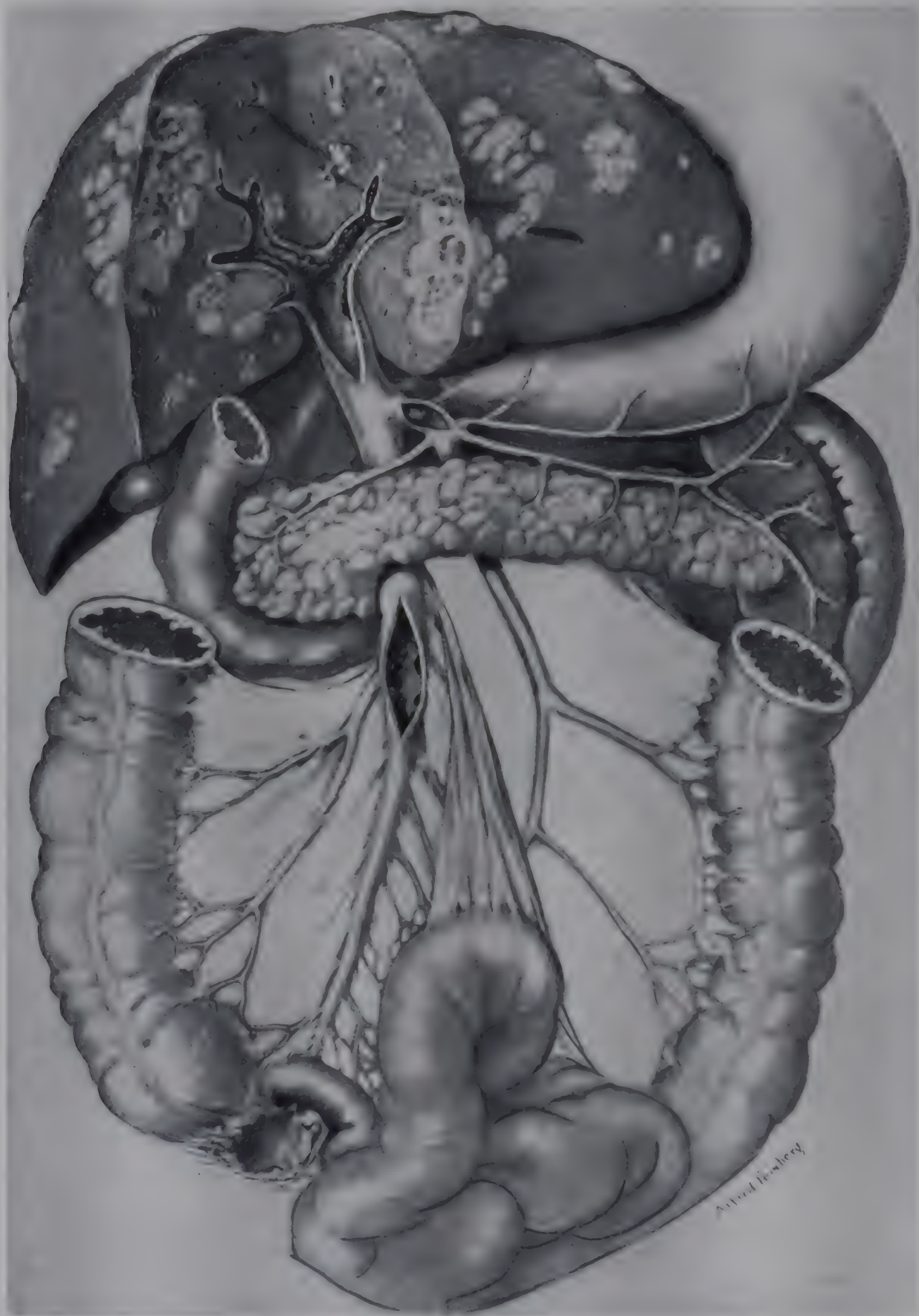


Fig. 157. Suppurative pylephlebitis arising from appendiceal abscess. Numerous abscesses in the liver. (MacCallum.)

Acute Nonspecific Inflammation of the Mesenteric Lymph Nodes

In some patients, particularly children with the signs and symptoms of acute appendicitis,

and edema with infiltration of leukocytes, rarely with abscesses. Cultures of the tissues give inconstant findings; many are sterile. A few patients give a history of a preceding enteritis or respiratory infection, but in most

the disease is clinically primary. Recurrence is observed in about a fourth of the patients (Postlethwait and Campbell).

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XXXVI

Miscellaneous Infections Caused by Intestinal Bacteria

The gastro-intestinal canal of the fetus in utero is sterile. During birth, the bacteria of the vagina are transferred to the mouth of the infant, and within twenty-four hours have traveled the length of the intestine and established themselves in the intestinal content.

In the adult, the empty stomach is usually sterile and the bacteria introduced with food, except for a few resistant types, are rapidly killed by the gastric juices. If there is hypomotility or obstruction, as in carcinoma of the stomach, the retained food may contain bacteria.

In the duodenum and upper jejunum, there are few bacteria aside from occasional enterococci (Rantz and Kirby). Beginning in the lower jejunum, there is a progressive increase in the number and variety of bacteria, with a maximum in the colon. The most common are: bacilli of the colon-aerogenous group (lactose fermenters); enterococci, staphylococci, *Clostridium welchii*, aciduric bacteria of the genus *Lactobacillus*, thermophilic bacteria, spirochetes, and yeasts.

The Barrier of the Intestinal Mucosa. Under ideal conditions, the mucosa of the intestine serves as an impermeable barrier between the bacteria of the lumen and the tissues of the body. The occasional bacterium that invades the body is destroyed in the liver and spleen. The barrier is, however, subject to change. Alkalinity of the upper small intestine, deficiency of vitamin B, and other factors will allow the intestinal bacteria to pass into the blood and lymph. In newborn children, the barrier is far less effective than in adults (Arnold; Smith).

Pathogenesis. In most instances of infection caused by the intestinal bacteria, the organisms enter the body through the intestinal wall. In a few, there is contamination of the skin or the orifices of the body with fecal material. This is especially true in young infants, in

whom contamination of the mouth and nose in the birth canal and contamination of the mouth by bath water are important modes of transmission.

Diseases Caused by Bacteria of the Proteus Group

Members of the genus *Proteus* are widely distributed in nature in close relation to the decomposition of organic matter. They are found in the gastro-intestinal tracts of some healthy individuals. They are rarely encountered as the primary causative agent of disease, but are usually secondary invaders in association with streptococci and staphylococci.

Pathologic Anatomy. Pathologic changes produced by *Proteus* are of two types: acute necrotizing suppurative inflammation, and food poisoning. The suppurative inflammations are most common in the urinary tract, in the middle ear and related structures, and in the gastro-intestinal tract, especially in lesions associated with perforation. In the urinary tract notable lesions are abscesses of the prostate and pyelonephritis. Septicemia may follow instrumentation, as with a cystoscope, or ureteral catheterization (MacKenzie and Hawthorne); or may be dependent on thrombophlebitis of the smaller radicles of the renal vein (Hirsch and Shapiro). In otitis media caused by *Proteus vulgaris* there is widespread necrosis of the soft tissues and of the bone, with extension to the mastoid and occasionally to the lateral sinus and meninges. The *Proteus* organism may be a primary invader or secondary to a preexisting suppurative inflammation with streptococci or staphylococci (Neter and Chait). In meningitis there are frequently abscesses in the substance of the brain, with numerous small foci of hemorrhage and necrosis. The predominant cell is

the polymorphonuclear leukocyte. Recovery is unusual (Meltzer). In peritonitis associated with perforation, and occasionally in wounds, the *Proteus* organism may play a primary role in establishing a suppurative inflammation (Bengtson).

***Proteus morganii*.** This organism, first isolated from the stools of children with summer diarrhea, is sometimes classified in the genus *Salmonella*. There are, however, a number of biochemical and antigenic properties which directly relate it to the *Proteus* group. We have seen cases of ulcerative colitis in children in whom the only organism of even doubtful pathogenicity which could be isolated was *Proteus morganii*. Further studies are needed in this field.

Diseases Caused by Pseudomonas Aeruginosa

The bacteria of this species are generally of low pathogenicity, and are secondary invaders in wounds and other inflammations. But they may, on occasion, produce primary disease, such as otitis media, enteritis, endocarditis, and meningitis.

Pathologic Anatomy. The general pathologic lesions produced by *Pseudomonas aeruginosa* are necrosis of tissue, abscess formation, massive infiltration with polymorphonuclear leukocytes, acute suppurative arteritis of the surrounding vessels, and massive bacterial colonization.

In the skin, especially about the anorectal and genital regions and umbilicus of children, deep ulcers with indurated, elevated, undermined edges are formed—a condition known as “ecthyma gangraenosum” (Epstein and Grossman). Occasionally in adults a chronic ulcerative form of pyoderma is associated with bacteria of this species, either as secondary or primary invaders (Yap).

In the rectum and colon, especially in association with inflammation of the perineum, the organism produces a proctitis, with necrosis of the mucosa and submucosa and massive bacterial colonization. The color of the necrotic tissue is bluish green (Kline and Maschke).

Inflammations of the ear, characterized by the formation of a green or yellowish green pus, may involve only the external structures—external otitis (Morley), or may invade the

middle ear and the mastoid antrum. In the urinary tract typical pyelonephritis with multiple abscesses is occasionally seen (Greig). Rare lesions are osteomyelitis (Schein), arthritis (Bishop), and bronchopneumonia. In many of the above types of infection bacteria may invade the blood stream, with a resulting vegetative endocarditis; or may erode the bone separating the ear from the meninges, and set up a leptomeningitis (Slutsky and Matlin; Allin). Pseudomonal meningitis also occasionally follows lumbar puncture.

Diseases Caused by Klebsiella Pneumoniae

Disease resulting from the pathogenic activity of *Klebsiella pneumoniae*, or Friedländer's bacillus, is most common in the gastro-intestinal tract (Baehr, Schwartzman, and Greenspan). The bacterium is not infrequently found in nasopharyngeal secretions and stools of healthy persons, and the causal relation of the bacterium to disease in these areas should be carefully evaluated.

Causal Agent. *Klebsiella pneumoniae* grows readily on all culture media. Immunologically three distinct types are recognized: A, B, and C. A heterogeneous Group X includes the few remaining strains (Julianelle). Group A organisms are the cause of 70 per cent of disease in man. The separation into the types depends on a specific carbohydrate in the capsular material. This carbohydrate is excreted in the urine in severe infections, and may be useful in diagnosis. Agglutinins and precipitins are formed by patients with manifest disease.

Pneumonia. In many respects pneumonia caused by Friedländer's bacillus is similar to pneumococcal pneumonia. The majority of cases show a lobar distribution. The lung lobe is voluminous and completely fills the pleural cavity. There is a small amount of fibrinous exudate over the surface. The architecture of the lung is obscured by a uniform, gray, consolidation. A large amount of thick viscid fluid can be expressed from the cut surface and the lung parenchyma is friable. The mucinous cut surface and the friability make possible a gross diagnosis of pneumonia caused by Friedländer's bacillus. Microscopically, an exudate is usually observed, filling the smaller bronchioles and the alveoli, with

the mononuclear cell predominating; while a few cases show polymorphonuclear leukocytes. There are immense numbers of large bacilli within the alveoli and in the alveolar walls. Fibrin is inconspicuous. Many alveolar walls show early necrotic change (Olcott; Julianelle).

About 1 per cent of clinical lobar pneumonia is due to Friedländer's bacillus. The disease occurs most frequently in adults, and particularly in those who are debilitated from some other cause. The mortality averages 85 per cent. Most of the pneumonias in man are

exact diagnosis must rest on bacteriologic studies.

Diseases Caused by Bacteria of the Coli-Aerogenes Group

The lactose-fermenting coliform bacilli may be divided into two great groups. One group, typified by *Aerobacter aerogenes*, gives a positive Voges-Proskauer reaction, a negative methyl red test, and forms a gas with carbon dioxide and hydrogen in a ratio of 2 to 1. It is rarely found in the intestine,

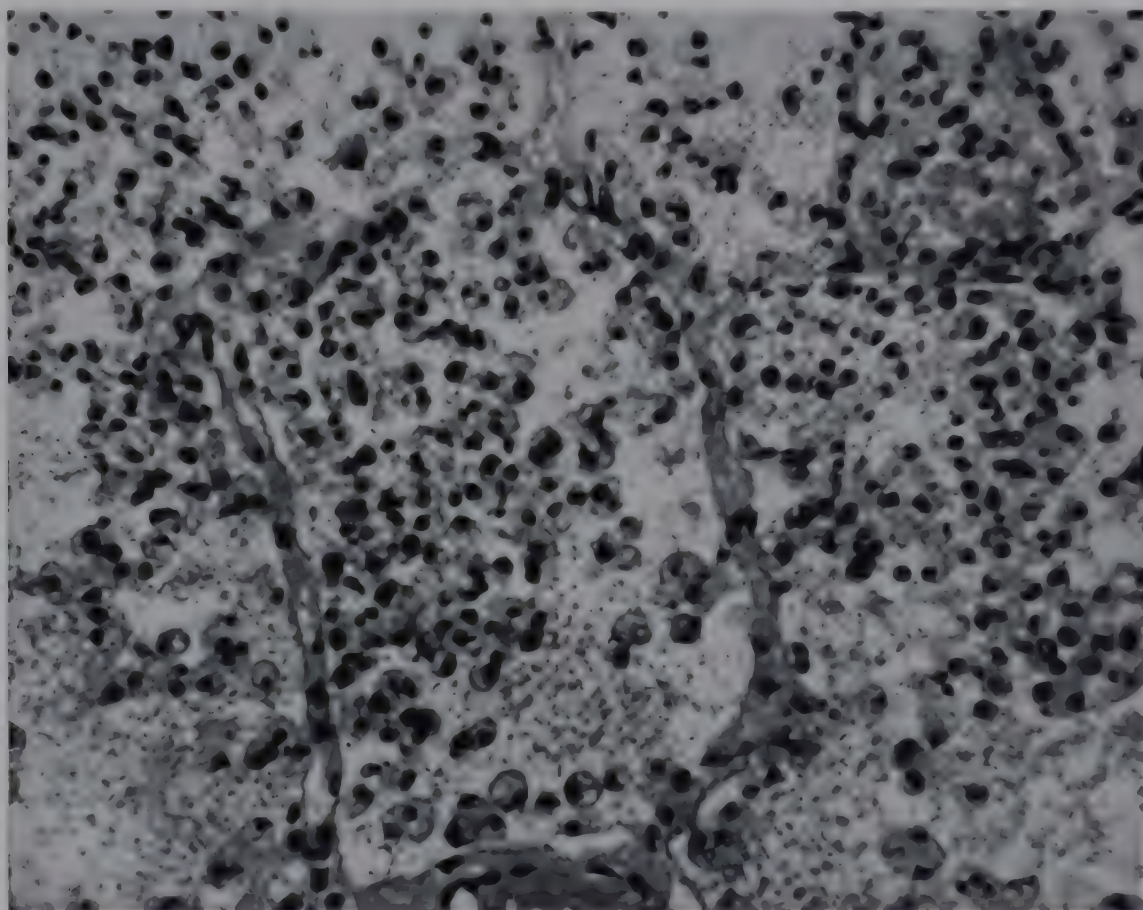


Fig. 158. Pneumonia caused by the Friedländer bacillus.

due to organisms of type A, and some success has followed the use of a specific serum (Bullock, Chess, and Friedman; Julianelle). In some patients following recovery from a pneumonia caused by *Klebsiella pneumoniae* there is residual fibrosis and cavitation similar to that of pulmonary tuberculosis (Collins).

Extrapulmonary Lesions. Diseases caused by *Klebsiella* outside the lung include hepatic abscess, sinusitis and mastoiditis (Profant), cystitis and prostatitis (Pfeiffer), salpingitis (Scheyer), meningitis (Ransmeier and Major), cholecystitis, appendicitis with a fecal fistula (Baehr, Schwartzman, and Greenspan), osteomyelitis, and keratitis (Chang). In none of these is the pathologic picture either grossly or microscopically characteristic, and the

but is commonly present on plants and grain and in water and soil. The second group gives a negative Voges-Proskauer reaction, a positive methyl red test, and forms a gas with carbon dioxide and hydrogen in a ratio of 1 to 1. It is typified by *Escherichia coli*, and is present in the intestine.

The most common lesions from which coliform bacteria are recovered are appendicitis, peritonitis, cholecystitis, and infections of the urinary tract. The first two of these have been discussed in the preceding chapter. Cholecystitis and pyelonephritis will be considered in later chapters (pp. 621 and 749).

Diarrhea in Infants and Children. Most instances of diarrhea in young children are specific infections, such as bacillary dysentery.

Despite the most diligent study, no bacteria other than those normally present can be cultured from the stools in some cases. In order to explain these cases, two possibilities have been proposed: (1) proliferation of colon bacilli in the upper intestine, and (2) change of the bacterial flora, with a preponderance of acid-forming bacteria. It is difficult to be certain, in those cases where *Escherichia coli* is present in the upper intestine, whether it is the cause or the effect of the diarrhea. It is possible that some examples of epidemic diarrhea in newborn infants result from invasion of the upper jejunum by coliform bacilli (Anderson and Nelson).

Miscellaneous Lesions. Rare conditions caused by the colon bacillus include otitic infection with or without sinus thrombosis and cerebral abscesses (Feldman), pneumonia (Dubin and Kerby), conjunctivitis (Johnston), and food poisoning. Meningitis in the newborn is most frequently caused by *Escherichia coli* and associated necrotizing otitis media in many cases suggests the upper respiratory tract as the portal of entry (Barrett, Rammelkamp, and Worcester). In endocarditis, the vegetations frequently spread from the valve to the adjacent chorda tendineae and atrial wall. Emboli, with petechiae and infarcts, are the rule (Harries and Burtenshaw).

Diseases Caused by Bacteria of the Genus Bacteroides

This genus of bacteria is not well understood, but there are apparently two clearly identifiable species which are capable of producing disease in man, *Bacteroides fragilis* and *Bacteroides funduliformis*. Some are gram-negative and some are gram-positive. They are normal inhabitants of the gastro-intestinal tract.

Pathologic Anatomy. The most common lesions in man are septicemia following throat infections and operation on the intestine, and meningitis secondary to otitis media (Smith and Ropes).

The abscesses formed in the liver, lungs, and periurethral tissue are similar to those caused by the pyogenic cocci, but there are certain distinguishing characters. In the liver the abscesses tend to be large and multilocu-

lar. The exudate within the abscesses is thick, tenacious, and purulent. In smaller lesions, the necrotic tissue resembles the caseous necrosis of tuberculosis, and is white or light yellow in color. Typically there is a peculiar odor resembling that of butyric acid. In most cases there is a well-developed capsule of fibrous tissue about the abscesses. The predominant cell is the polymorphonuclear leukocyte.

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XXXVII

General Considerations of Syphilis

Venereal diseases constitute a group of diseases whose causes vary from viruses to bacteria to spirochetes. They have in common the fact that their transmission, in the majority of cases, is by sexual intercourse. Included in the group are syphilis, gonorrhea, chancroid, venereal lymphopathy, venereal fusospirochetosis, and condyloma acuminata.

The relative importance of the individual diseases is difficult to estimate and the figures

based on a purely clinical diagnosis, on the percentage of positive Wassermann reactions in a large representative population, or on histologic findings of syphilis in autopsy material. The composite Table 20 serves to indicate the general trend of the published reports in various parts of the world.

Transmission. Syphilis is transmitted predominantly by sexual intercourse, as testified to by the fact that 97 per cent of chancres in

TABLE 20. INCIDENCE OF SYPHILIS

Type of Patient	Criterion	Number Observed	Per Cent Positive
White, drafted men in United States—World War II (Vonderlehr and Usilton)	Serologic	1,670,519	1.74
Colored, drafted men in United States—World War II (Vonderlehr and Usilton)	Serologic	225,259	25.23
Pregnant women—State of Massachusetts (Nelson)	Wassermann	7,755	5.1 (+ 4.8 doubtful)
Large group of population of Puerto Rico—urban and rural (Mandry)	Wassermann	32,305	6.7
Hospital patients, Nanking, China (Wang, Shen, and Chang)	Serologic	3,898	27.0
Routine autopsies—University of Michigan, Ann Arbor (Warthin)	Histologic	750	40.0
Routine autopsies—University of Minnesota (Bell)	Anatomic	27,872	2.77
Routine autopsies—Bellevue Hospital, New York City (Symmers)	Anatomic	4,880	6.5
Routine autopsies—School of Tropical Medicine, Puerto Rico (Koppisch)	Anatomic	1,000	8.1

vary in different parts of the world, in different races, in different economic and social strata, and in different years. It is probable that in the civilian populations of the United States and Britain gonorrhea constitutes 65 per cent to 75 per cent of venereal disease, syphilis about 10 to 20 per cent, and chancroid 2 to 5 per cent.

Syphilis in General

Incidence. There are many criteria for the diagnosis of syphilis. The incidence may be

men are on the skin of the genital organs. In women the situation is probably the same, but the sometimes hidden location of the chancre in the recesses of the vulva and the vagina results in higher reported percentages of extragenital chancres—20 per cent. Prostitutes constitute the great focus of the disease. Of 3800 women arrested in New York City for sexual crimes, predominantly prostitution, 58 per cent had syphilis, gonorrhea, or both (Clarke).

The extragenital transmission of syphilis is usually through kissing, as is shown by the

location of about 70 per cent of all extra-genital chancres on the lips (Clarke). Remarkable examples of small epidemics in a family have been described (Rowntree and Hendon). Transmission through inanimate objects, as towels and toilet seats, is extremely rare, since the spirochete is unusually sensitive to drying and to a change in temperature.

In adults about 3 per cent of all instances of syphilis are congenital in origin (Turner). Details of the transmission from mother to fetus are described under "Congenital Syphilis."

⑤ *Transmission by Blood Transfusion.* The spirochete of syphilis is present in the blood from time to time and the transfusion of blood from a person with a positive Wassermann reaction may be dangerous. In most instances the manifestations of secondary syphilis appear three to twelve weeks following a transfusion. There is much less likelihood of transmission from a person with tertiary syphilis than from a person with primary or secondary syphilis (Jones, Rathmell, and Wagner).

Reinfection. Before the discovery of the specific arsenicals by Ehrlich in 1910, examples of a second infection in syphilitic persons were extremely rare. After 1910 examples of undoubted reinfection were reported and by 1928, 229 cases were available for analysis (Halley and Wassermann). There seems little question that the incidence of reinfection is directly related to the elapsed interval of time between the first infection and the initiation of treatment. Of 83 patients with reinfection, virtually all had been treated for their first infection before the end of sixteen weeks, and 82 per cent before the end of the eighth week. Reinfections are never observed with late lesions of the central nervous system or of the cardiovascular system. Brown and Pearce found that if curative doses of arsphenamine were given to rabbits early in the course of primary infection, reinfection was possible. Control animals with an untreated primary infection were completely resistant to a reinfection. All the available evidence indicates that the possibility of a reinfection does not depend on eradication of the treponema from the body (complete cure) as was originally thought, but only on modification of the first infection by early treatment.

Tropism of the Treponema. There is suggestive evidence, not convincing, that different strains of the treponema have predilection for

certain tissues such as the nervous system and skin (Moore and Kemp). On the other hand, there is equal evidence that syphilis in some families, regardless of source, tends to invade certain tissues, indicating a familial predisposition (Moore and Keidel).

The fact that the treponema produces frequent lesions in some organs and not in others may be related to the hyaluronidase or spreading factor in the former (Scott).

Syphilis in Experimental Animals. Syphilis has been experimentally transmitted from man to monkeys and to rabbits, but the spontaneous disease has never been observed in any species except man. The rabbit has a superficial infection of the genital region caused by *Treponema cuniculi*, but it is not comparable to human syphilis, and there is no immunologic relation between the two organisms. Attempts to transmit syphilis to animals other than the monkey and the rabbit have not been successful. In both of these species the disease runs a course not unlike that of the disease in man, with a primary lesion, secondary manifestations in the skin, mucous membranes, and lymph nodes, and to a limited extent late involvement of the viscera with chronic productive lesions.

Immunity in Syphilis—The Wassermann Reaction. Laboratory search with both in vitro and in vivo methods has given little evidence that immune bodies are developed in the course of syphilitic infection similar to those observed in bacterial and viral diseases. When Wassermann, Neisser, and Bruck developed what is now known as the Wassermann test, a pure culture of the treponema was not available, and they used as an antigen an extract of the liver in congenital syphilis, in which treponemas are extremely abundant. The success of the test led them to believe that it represented a true antigen-antibody reaction between the serum and the extract of the treponema. However, it was soon shown that an antigen could be prepared from normal liver or from heart muscle which had an equal degree of specificity. One must thus conclude that the usual complement fixation and precipitin reactions are physicochemical reactions depending upon the lipid substances that develop in the serum during the course of syphilis or yaws (Chesney, Moore and Eagle).

Anatomically Latent Syphilis. In clinical medicine it is customary to make a diagnosis

of latent syphilis in a person who has no signs or symptoms of syphilitic disease, but who has a positive Wassermann reaction. In different laboratories the percentage of cases with no histologic evidence of syphilis but with a positive Wassermann reaction varies from 1 per cent to 15 per cent, largely depending on the criteria used for the diagnosis of syphilis. It must be acknowledged that there is a certain small percentage of individuals who have syphilitic infection but not syphilitic disease.

Coexistence of Pulmonary Tuberculosis and Syphilis. On the basis of both clinical and autopsy observations these two diseases are more frequently associated than would be expected on the basis of coincidence. In the material at the Baltimore City Hospital there was a coexistence in 14.2 per cent. More careful scrutiny shows that tuberculosis has no influence on the course of syphilis, and that latent syphilis has no effect on the course of pulmonary tuberculosis; but there is good reason to believe that active syphilis has a decidedly unfavorable influence on the course of pulmonary tuberculosis. The reason for this relation is not apparent (Habliston and McLane).

Coexistence of Syphilis and Cancer. Carcinoma of the buccal cavity in persons with syphilis is more common than in others, but the mechanism of the relation is not understood.

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XXXVIII

Congenital Syphilis

During the nineteenth century congenital syphilis was frequently seen both clinically and pathologically. Since the introduction of the specific arsenicals for treatment there has been a decreasing number of instances of the condition. In 1920 Jeans and Cooke in St. Louis found congenital syphilis in 1.8 per cent of white families of the poorer classes, 1 per cent of white families of the better classes, and 15 per cent of colored families. Calculated from the number of families in each group in the city of St. Louis, this gives an average incidence of 2.8 per cent (Turner).

Pathways of Infection—Colles' Law. Profeta's Law. It seems clear that transmission of syphilis from father to fetus is impossible without simultaneous or previous infection of the mother. The treponemas in the mother invade the placenta or pass directly across the placenta in the blood and lodge in the various tissues of the infant. From the early clinical study of congenital syphilis two so-called "laws" have been handed down. The first, Colles' law, states that the mother may give birth to a syphilitic child without having the disease herself. Actually Colles said this: "I have never seen or heard of a single instance in which a syphilitic infant (although its mouth be ulcerated), suckled by its own mother, could produce ulceration of her breasts; whereas very few instances have occurred where a syphilitic infant has not infected a strange, hired wet nurse and who has been previously in good health." This means nothing more than that such a mother has latent syphilis and is not reinfected by her infant. The second, Profeta's law, states that a healthy child may be born of a syphilitic mother and is then immune, at least until there is a complete exchange of its primary cells. On superficial observation this statement is true, but a Wassermann reaction or

histologic study of this child would leave no doubt that it has syphilis. Both of these laws deal only with clinical appearances, and were postulated before the development of the concept of latent syphilis, both in adults and in children.

Syphilis of the Placenta. The classical syphilitic placenta is large and moderately firm, and may constitute one-third or one-half of the total weight of the fetal structures. Careful examination of the villi reveals that they are short and club-shaped and do not separate under water into the normal delicate architecture. There is an increase of fibrous tissue within the individual villi and slight infiltration with lymphocytes and mononuclear cells. The walls of the blood vessels are thickened by a proliferation of fibrous tissue in the intima. The arteries and the veins in the umbilical cord are thickened by proliferation of the intima. The tissue between the vessels shows infiltration with leukocytes and small foci of necrosis. Recently, more precise histologic studies have shown that this type of placenta is not infrequently seen in the absence of demonstrable syphilis. It is highly probable that many of these cases are in reality fetal erythroblastosis and not syphilis. Spirochetes are occasionally demonstrated, but usually in small numbers, and it may be said that the pathologic changes of syphilis of the placenta are yet to be established (McCord).

Time of Infection of the Fetus. Stains of the tissues of fetuses aborted, at various times during gestation, from syphilitic women who have not been treated show that no spirochetes are present before the fifth month. If it be assumed that it takes four to six weeks for the development of definite histologic lesions, it follows that infection of the fetus from the mother occurs at the middle or toward the

end of the fourth month. Abortion before this time cannot be directly attributed to the effect of syphilis on the fetus. It is of interest that these time periods correspond in general with the time of the degeneration of the syncytial layer of the placenta.

Influence of Pregnancy on Syphilis in the Mother. It has been repeatedly observed by clinicians that pregnancy may bring about remission of some of the outstanding symptoms of syphilis. If the infection with syphilis occurs at the time of conception or shortly

effects from the use of arsenicals during pregnancy.

Relation of Spirochetes to Pathologic Lesions. Frequency of Lesions. In the pathologic study of congenital syphilis it is necessary to distinguish between syphilitic infection and syphilitic disease, as enormous numbers of spirochetes may be demonstrated in the organs of a fetus without inflammation. This is well shown in the statistical study presented before the German Pathological Society in 1928 (Schneider-Darmstadt) (Table 21).



Fig. 159. *Treponema pallidum* in liver in congenital syphilis.

thereafter, the manifestations are mild or may be completely suppressed. Secondary manifestations in the skin are likely to be absent, and the patient will then give no history of having had either the primary or the secondary manifestations of syphilis when she is examined many years later for tertiary syphilis (Moore). It is highly probable that this influence is related to the large amount of estrogenic hormone in the fluids of the body during pregnancy (Kemp). On the other hand, the incidence of toxemia of pregnancy is about twice as great in syphilitic as in nonsyphilitic women. When properly treated, a syphilitic mother may give birth to a healthy child, and the percentage of stillbirths under these conditions is about the same as in any control series. Histologic studies of the organs of the newborn infant give no evidence of injurious

This table does not include lesions of the bones which are probably the most common, and are present in some forms in about 75 per cent of all syphilitic infants. It does show that the liver, pancreas, and lung are the most important organs for the pathologist to examine for histologic lesions, and that a stain for spirochetes on the liver gives significant information.

Pathologic Changes of Congenital Syphilis

When lesions develop there are four general types: (1) an acute inflammation characterized by infiltration with polymorphonuclear leukocytes, edema, and hyperemia; (2) a sub-acute or chronic interstitial inflammation with infiltration with leukocytes and plasma cells;

gummatous necrosis similar to that of all gummas; and delay of embryonic development. This last is exemplified in many of the organs. The osteochondritis of bone prevents the growth of bone; the inflammation of the pancreas is associated with incomplete development of the acini; and the kidneys show an unusual number of immature tubules and glomeruli in the peripheral part of the cortex.

Hutchinson's Triad. This group of three lesions originally described by Hutchinson—notched permanent incisors, deafness, and interstitial keratitis—has received great prominence, but actually is not common. All appear months or years after birth and are of no

duction of the characteristic “salt and pepper fundus” (Friedenwald; Green).

Ears. Although nerve deafness is part of Hutchinson's triad, it is probable that syphilis is the cause of less than 1½ per cent of all deafness. In the *inner ear* there is an inflammation of the cochlea, with miliary gummas in the tissues. The overproduction of fibrous tissue leads to stenosis and ectasia of the cochlear duct, with atrophy of the specialized epithelium of hearing. About the *semicircular canals* there is a proliferation of the periosteum, a new deposit of bone, and a marked narrowing of the lumen of the canals. In the *spiral ganglion* and in the *eighth nerve* there

TABLE 21. RELATION OF SPIROCHETES TO PATHOLOGIC LESIONS IN CONGENITAL SYPHILIS

	Spirochetes			Lesions		
	Stillborn (Per Cent)	Dying Soon after Birth (Per Cent)	Young Infants (Per Cent)	Stillborn (Per Cent)	Dying Soon after Birth (Per Cent)	Young Infants (Per Cent)
Liver	100	84	39	20	38	46
Pancreas	84	83	20	23	91	12
Lung	95	91	25	18	50	10
Spleen	96	84	33	15	38	33
Heart	83	83	29	0	8	4
Kidney	90	84	38

value in the establishment of an early diagnosis.

Eyes. About 50 per cent of children with congenital syphilis have some lesion of the eye. The most important are interstitial keratitis, iritis, and chorioretinitis. In interstitial keratitis the *cornea* is opaque and granular, and is increased in thickness, and richly vascularized. Microscopically, heavy infiltration into all layers of lymphocytes and plasma cells is seen. In association with the capillary vessels there are numerous fibroblasts. The corneal epithelium is degenerated or absent. The end result of the pathologic process is the replacement of the cornea by dense collagenous fibrous tissue through which light will not pass, and the victim is blind in both eyes, as the process is almost always bilateral. The inflammation of the *iris*, *choroid*, and *retina* show an essentially similar process. Destruction of the choroid and retina leaves white, circumscribed scars, while destruction of the choriocapillaris leads to migration of the pigment and the pro-

are infiltration with lymphocytes and plasma cells and slight fibrosis. There is a similar inflammatory process in the body of the *petrous bone*, and at times small or large gummas (Mayer and Fraser).

Teeth. The third of Hutchinson's triad is the characteristic hypoplasia of the *deciduous second molar* and of the *permanent incisors* and *first molar teeth*. These are known as “notched” or “screwdriver” incisors and “mulberry molars.” The reasons for this selective involvement are clearly shown in Fig. 160, taken from the work of Karnosh. The stippled area represents the time when there is an active syphilis in the infant, and the enamel of the involved teeth is deposited in large part during this period. The typical *incisor* is shorter than normal and the biting edge is distinctly narrower than the gum margin, because the enamel at the biting edge laid down during the first year of life is hypoplastic, while the enamel laid down in subsequent years is more normal. The typical *molar* tooth is also

small; the normal cusps are poorly formed and close together, and about the occlusal surface there are numerous small pseudo-cusps. The explanation is the same: the enamel cap deposited in the first year of life is hypoplastic, and the subsequent more normal deposits must be irregularly placed and buckled in order to form a tooth (Karnosh). It is more probable that the hypoplasia is the expression of a general or specific deficiency of growth rather than the direct result of the invasion of the enamel organ by the spirochete (Hill). The characteristic changes may be observed in x-ray pictures of unerupted teeth (Sarnat, Schour, and Heupel).

there is an increase in the thickness of the zone of proliferate cartilage. These observations suggest that the syphilis has interfered with the destruction of the calcified cartilage and the replacement of it with bone, but not with the progression of changes in the cartilage.

The next stage in osteochondritis is the appearance of a zone of metaphyseal rarefaction, consisting of a decreased number of thin trabeculae with abundant fibrotic marrow. Spirochetes may be demonstrated in this fibrous tissue. There is a slight infiltration with lymphocytes. The explanation of this stage is similar to that of the first—a de-

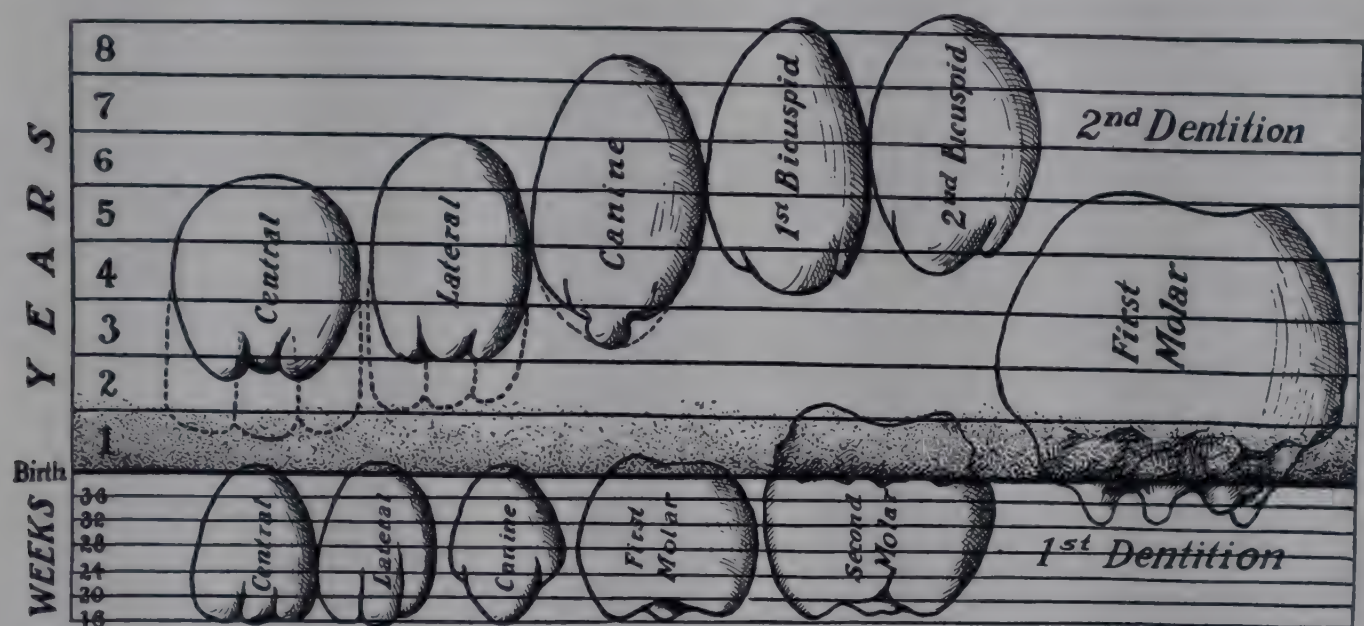


Fig. 160. Table of inception and duration of enamelization of the first and second dentition, showing the time factor of congenital syphilis and the manner in which it affects the second deciduous molar, the first permanent molar, and the enamel organs of the incisors and the cuspid. The intensity of the stippling in this syphilitic zone represents the degree of severity of effect. (From diagram of Karnosh, L. J.: Arch. Dermat. & Syph., Vol. 13.)

Bones. Lesions of the bones in congenital syphilis are conveniently divided into two types: the lesion found at or shortly after birth, termed "osteochondritis," and the lesions observed in late congenital syphilis, which do not differ essentially from those of acquired syphilis.

Syphilitic Osteochondritis. The earliest lesion of syphilitic osteochondritis is seen in x-ray pictures of the long bones of newborn infants as an increase in the thickness of the zone of calcification at the ends of the bones. The metaphyseal region is broader than normal, whitish yellow instead of pink, and gritty. Microscopically this zone is seen to contain a great number of interlocking tiers of calcified cartilage. There is little evidence of erosion of cartilage by the primitive marrow and only slight osteoblastic activity. Occasionally

creased rate of formation of bone, and probably an increased resorption.

In more advanced lesions there is active proliferation of the primitive marrow, with numerous fibroblasts and blood vessels filling the cartilage canals. In the region of the primary spongiosa there is a chaotic mixture of cartilage cells and of calcified and uncalcified cartilage matrix, free or attached to the epiphyseal cartilage. This results in an irregular line at the metaphysis, seen both roentgenologically and in section. There is also an active resorption of the trabeculae of the spongiosa, and replacement by fibrous tissue infiltrated with lymphocytes and plasma cells. There are occasional small gummas. From the fibrous tissue small foci of metaplastic bone may be formed (McLean).

The lesions are most conspicuous in those

bones most actively growing. These are in order: distal end of femur, distal and proximal ends of tibia, distal and proximal ends of radius and ulna, the ends of the metacarpals, and the proximal ends of the phalanges.

EPIPHYSEAL SEPARATION. As a result of the replacement of the primary spongiosa with connective tissue and a deficiency of bone in this region, some unusual stress or trauma may displace the epiphysis to one side, most commonly in the arm. This is followed by attempted repair and the new formation of metaplastic bone from the connective tissue. From other types of stress the metaphysis may be impacted into the diaphysis. These lesions are known clinically as "pseudoparalysis of Parrot."

OSTEOMYELITIS. DACTYLITIS. Focal osteomyelitis, an oval or spherical area of resorption of bone and replacement by connective tissue infiltrated with lymphocytes and plasma cells, may be present. It is evident on the x-ray plate as a punched-out, rarefied area. It is most common on the upper end of the tibia and in one or more of the carpal, metacarpal, or first and second phalangeal bones. In the bones of the hand there is a fusiform swelling of the shaft of the bone and of the fingers, producing the highly characteristic picture of syphilitic dactylitis. Very rarely there is new formation of bone in the periosteum or in the shaft, with eburnation similar to that seen in acquired syphilis.

SYPHILIS OF THE FLAT BONES IN INFANCY. Extensive syphilitic involvement of the flat bones in infants is not common. The most frequently observed lesion is a diffuse or focal resorption of the flat bones of the skull and replacement by fibrous tissue.

Bone Change in Late Congenital Syphilis. The pathologic appearance of the *periostitis* and of the *osteitis* of late congenital syphilis is similar or identical with that of acquired syphilis. Distinctive lesions are an osteitis of the inner third of the clavicle, with palpable expansion of the bone (Yang), gummatous destruction of the vomer with resulting "saddle nose," and periostitis of the tibia with the formation of the "saber shin."

Nervous System. Involvement of the nervous system is not common in early congenital syphilis. There may be a diffuse or focal *meningitis* or distinctive lesions of the *blood vessels* or a *gumma*. All are similar to lesions in acquired syphilis.

Juvenile Paresis. The brain in juvenile paresis is pathologically identical with that in adult paresis (p. 331). The onset is usually between the fifth and the ninth year, and it is slightly more common in boys. The course varies from two to five years, and treatment is of little avail (Wile and Hand).

Juvenile Tabes Dorsalis. Tabes dorsalis in congenital syphilis is extremely rare, and is seen only about one-tenth as frequently as juvenile paresis. The pathologic changes are the same as those of tabes in acquired syphilis (p. 332). The average age of onset is fourteen years, and the course is extremely chronic. The signs and symptoms are the same as those in adults, except that ataxia is inconspicuous (Parker). Tabes may also occur in children as the result of syphilis acquired during infancy (Lasarew).

General Effects of Congenital Syphilis on Mental Development. Mental deficiency or frank idiocy is observed in children with congenital syphilis, but there has not been sufficient clinicopathologic study to make any exact statements.

Cardiovascular System. Significant lesions of the cardiovascular system are unusual in congenital syphilis, and are limited to aortitis and myocarditis. Pathologic changes are the same in the aorta as those in acquired syphilis (p. 321) (Norris; Neiman and Mark). The usual age of onset of symptoms is nine to fifteen years, but histologic lesions have been observed in stillborn infants (Klotz). The myocarditis of congenital syphilis is essentially a microscopic lesion. The heart may be slightly dilated, and on section of the muscle irregular yellow foci are occasionally observed. Histologically there are two types of reaction, an acute and a chronic, corresponding to an infiltration of leukocytes and plasma cells, respectively. There is an intense edema, but no proliferation of connective tissue. Many of the myocardial fibers show advanced fatty degeneration.

Respiratory System. One of the most common clinical signs of congenital syphilis is a mild, chronic coryza, commonly known as "snuffles." The mucous membrane is swollen and red, and microscopically a diffuse infiltration with leukocytes, lymphocytes, and plasma cells is seen. In the most advanced stages there is necrosis of the mucous membrane and ulceration. The necrosis may extend into the cartilage and bone, with de-

struction of the septum and of the lateral walls of the nares. Secondary infection is common.

Lungs—*Pneumonia Alba*. Significant involvement of the lungs usually leads to death during the first few days or weeks of life. Pathologic changes may be divided into a diffuse and a focal type of lesion. The diffuse lesion constitutes what is termed “pneumonia alba” or “white pneumonia.” The lungs are large and firm, and over the surface of the pleura there is a fine fibrinous exudate. Microscopically the peribronchiolar tissues in the alveolar septa are conspicuous and are seen to be heavily infiltrated with lymphocytes, plasma cells, and a few leukocytes and eosin-

the lumen. Microscopically, central necrosis of the mucosa and submucosa, with surrounding proliferation of fibrous tissue, is observed. The arteries are thickened. At the edge of the necrotic tissue there are giant cells and lymphocytes. Perforation of the necrotic tissue with a resulting peritonitis has been reported.

Liver. The liver and the pancreas show the most significant and characteristic changes of congenital syphilis. The principal lesion of the liver is a diffuse interstitial hepatitis. The organ is enlarged and may constitute as much as one-twelfth of the body weight. It is firm and grayish brown. There may be a fibrinous or a fibrous perihepatitis. On cut section the

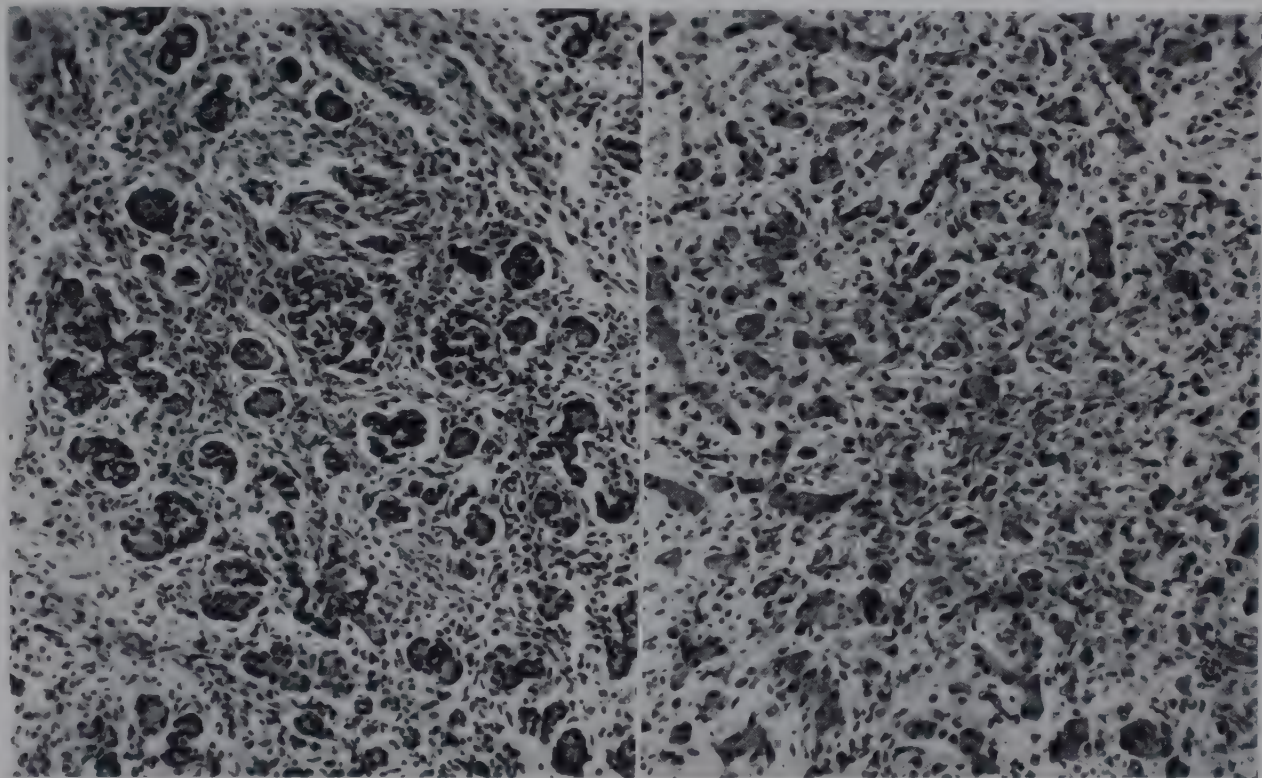


Fig. 161. Congenital syphilis of pancreas and liver.

ophils. The alveoli are small and lined by cuboidal cells. In all parts of the lung, there is an abundance of loose, mesenchymal-like, connective tissue. Within the alveoli there are numerous large mononuclear cells, the cytoplasm of which is finely vacuolated. Necrosis and the formation of gummas are unusual. The focal lesions are essentially the same except that the fibrous tissue is more collagenous, and central necrosis, that is, a gumma, is common.

Gastro-Intestinal Tract. Lesions of the mouth and pharynx are similar to the mucous patches of secondary acquired syphilis. The esophagus is rarely involved. In the stomach (Oberndorfer) and in the intestine (D'Aunoy and Pearson) small or large, yellow, plaque-like lesions are seen in the submucosa. In the intestine these show a tendency to encircle

architecture is obscured. There is a diffuse increase of a loose, collagen-poor connective tissue between the liver cords and between individual cells, which is infiltrated with leukocytes, lymphocytes, and plasma cells. Some of the hepatic cells are atrophic while others are large and multinucleated. In the sinusoids there are numerous foci of active hemopoiesis. Rarer lesions are gummas and diffuse interstitial inflammation about the hilum.

Pancreas. The changes in the pancreas are similar to those in the liver: a diffuse or focal interstitial inflammation and fibrosis. The lobules and acini are few in number and are separated by a dense connective tissue infiltrated with lymphocytes, plasma cells, and a few eosinophils. The ducts contain a few leukocytes. The periarterial tissues are fibrotic, but there is no significant endarteritis. The

islands of Langerhans are usually well preserved. Chronic interstitial inflammation in the salivary glands has been reported.

Urogenital Tract. Microscopically the kidney shows delayed development, and numerous immature tubules and glomeruli are present just beneath the capsule. There are throughout the cortex and medulla small foci of infiltration with lymphocytes and plasma cells. Rarely there are miliary gummas.

Spleen. Although the spleen is regularly large and firm in congenital syphilis, histologic changes are not pathognomonic. There

which are in part necrotic. There is a cellular infiltration with lymphocytes and plasma cells, and numerous islands of hemopoiesis (Fite).

Thymus—Dubois' Abscess. The most characteristic lesion of the thymus is the rare Dubois' abscess. In the central part of the organ, which is enlarged, there is a cavity filled with a thick yellow fluid. There is necrosis of the medulla of each lobule of the thymus, and coalescence of these produces the larger abscess. The cavity is lined by what appear to be epithelial cells, probably derived from the reticulum of the thymus (Simmonds).

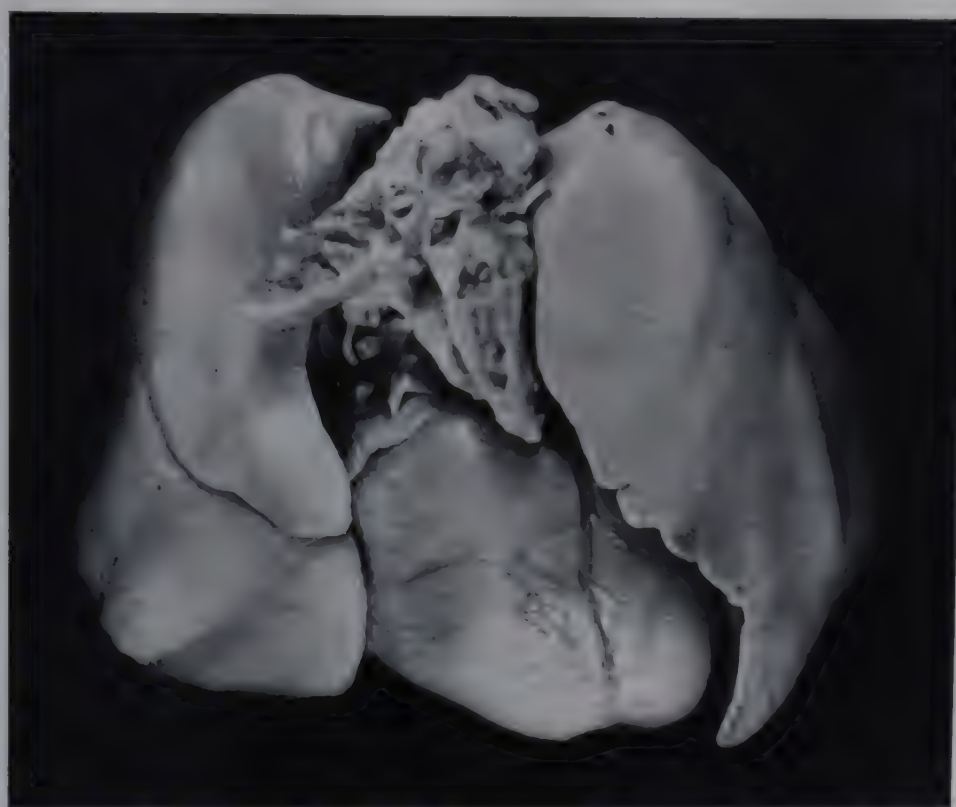


Fig. 162. Dubois abscess of the thymus.

is an increase of the reticulum and a thickening of the splenic cords of the red pulp. The smaller arterioles are thickened, and a perisplenitis, either fibrinous or fibrous, is common. In some instances there is active erythrophagocytosis, which may explain the anemia of congenital syphilis. In distinction from von Jaksch's anemia, or pseudoleukemia infantum, there is no myeloid metaplasia in the spleen (C. J. Watson).

Endocrine Glands. In the thyroid (Menninger), in the pituitary (Schmitt), and in the testes (Menninger), diffuse interstitial fibrosis with lymphocytic infiltration has been observed. In all, small gummas may occur.

Adrenals. The adrenal glands are usually large and firm, and there is an increase of fibrous tissue in the capsule and extending down between the cords of the cortical cells,

Skin. The superficial manifestations of congenital syphilis on the skin are well known, but they are really not as frequently observed as are many lesions of the viscera. In general they appear before the third to the sixth month of life.

Rhagades. "Rhagades" is generally used to designate both fissures and the resulting scars on the lip, chin, cheeks, suborbital ridges, and about the anus in congenital syphilis. The initial lesion is a diffuse infiltration of the dermis by lymphocytes and plasma cells. The epidermis is elevated, tense, and bright red or brown in color. Probably as the result of movement, the tense epidermis tears at right angles to the lines of force and a fissure is formed. The result is a linear scar which shows histologically an abundant collagenous tissue, devoid of elastic fibrils. The lesions usually

appear in the fifth to the seventh week of life, and are present in about 5 per cent of all congenitally syphilitic children (Strakosch).

Lesions on the Palms and Soles. One of the most common lesions of the skin in congenital syphilis is a hyperkeratosis and desquamation of the epidermis of the palms and soles. Histologically there is a slight infiltration and hyperemia in the dermis.

Nails. Perionychitis, with loss of all of the nails of both hands and feet, is occasionally observed in young children. In older children,



Fig. 163. Rhagades, perioral excoriations, lesions on the hands, and onychia in congenital syphilis. (Photograph by courtesy of Dr. Malcolm Cook.)

there is a characteristic ridging and bowing of the nails, which are a dirty gray color.

Other lesions of the skin are similar to those observed during the secondary or tertiary stages of acquired syphilis.

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XXXIX

Acquired Syphilis: Manifestations of the Primary and Secondary Stages

It is customary to recognize three stages in acquired syphilis in man: (1) the primary stage or chancre, (2) the secondary stage, with conspicuous lesions in the skin and mucous membranes, and (3) a tertiary stage, with pathologic changes in many tissues, notably in the cardiovascular system and in the nervous system. The first two stages may be designated collectively as early syphilis, in contrast with tertiary or late syphilis.

General Pathologic Changes of Acquired Syphilis. Two general types of pathologic changes result from the action of the treponema of syphilis in tissue: (1) a focal or diffuse chronic interstitial inflammation and (2) a characteristic granulomatous lesion known as the gumma.

In the last century it was believed that the gumma was the usual and most frequent manifestation of late syphilis. Careful histologic studies in the early part of this century made it evident that the gumma is really a rare lesion, and that chronic interstitial inflammation is the common manifestation of tertiary syphilis (Warthin).

Chronic Interstitial Inflammation. This type of lesion is most frequently seen in the leptomeninges, myocardium, aorta, pancreas, adrenals, and testes. It is characterized by focal or rarely by diffuse fibrosis, infiltration with lymphocytes and plasma cells, proliferative endarteritis, and loss of parenchymatous elements. *Treponema pallidum* in small numbers can be demonstrated in a significant percentage of these lesions (Warthin).

The Gumma. The gumma is a granuloma varying from microscopic size to several centimeters in diameter. The microscopic gummas may be multiple, but those from 1 to 2 cm.—the average size—are usually single, or at the most only two to five are found in any one organ. There are two essential parts: a central,

firm or elastic, gelatinous or hyalinized, necrotic mass, and a peripheral zone of inflammation and fibrosis. The necrosis is of the coagulation type and shadows of preexisting structures are evident. The peripheral zone has the characteristic and diagnostic features. Adjacent to the necrotic tissue is a zone of epithelioid cells and lymphocytes, separated by small capillary vessels. Multinucleated cells and giant cells are occasionally seen. Next peripherally is a zone of proliferating fibroblasts and capillary vessels, infiltrated with lymphocytes and plasma cells. At the extreme periphery in older gummas is a layer of dense collagenous connective tissue. Treponemas are present in small numbers.

The gumma differs from the tubercle in a number of respects: the type of necrosis, the absence of satellite granulomas in the circumferential zones of the larger lesions, the relative absence of giant cells, and the vascularization of the zone of epithelioid cells.

About one-half of all gummas are in the liver. The other half are found in many organs but are most frequent in the testes, brain, bone, and skin.

The Chancre

The chancre appears at the site of inoculation, after an incubation period of twelve to forty days. The first visible lesion is a small macule, which rapidly develops into a papule or nodule. At this stage there are acanthosis and perivascular infiltration of the dermis with lymphocytes and plasma cells. The connective tissue fibers are separated, the elastic fibers are well preserved, and the limits of the infiltration are sharp.

As the nodule increases in size the overlying epidermis becomes atrophic and is eventually lost, and an erosion forms. It is

at this stage that the typical Hunterian chancre is evident. It is a single lesion with erosion of the surface rather than ulceration. The erosion is sharply defined, is not undermined or ragged, and has a clean base. About the erosion there is firm induration, and a serous exudate may be expressed onto the surface. At the edges the epithelium is acanthotic. Nearer the center the rete is flattened, and the epidermis is edematous and is infiltrated with lymphocytes. In the underlying dermis the infiltration with lymphocytes and plasma cells is dense, and in the center the perivascular arrangement may no longer be visible. With

on the vulva does not mean that a chancre was not present at some time in the past.

Manifestations of Secondary Syphilis

The lesions of the secondary stage are found predominantly in the skin, mucous membranes, and lymph nodes. The gross and even the microscopic features are extremely variable. The classification of McCarthy includes macular, papular, and vegetating lesions, transitional forms, disturbances in pigment formation, and involvement of the adnexa of the skin.



Fig. 164. Chancre. Note the clean elevated flat base. (Photograph by courtesy of Dr. Malcolm Cook.)

the passage of time the plasma cells increase in relative number and the fibroblasts proliferate. The lymph vessels and the blood vessels are dilated. The endothelial cells and the subintimal fibroblasts increase in number and partly fill the lumen of the small vessels. There is also active proliferation of the adventitial cells and budding of capillaries. Treponemas are most abundant in the lumen and walls of the lymph vessels. In the connective tissue they are collected in small clumps.

After from three to eight weeks healing begins. The infiltrated cells gradually leave the region and the epithelium grows over the surface. The degree of scarring is variable, and the absence of a cicatrix on the penis or

Skin and Mucous Membranes. The basic microscopic appearance of all lesions of the skin and mucous membranes is the same: a cellular infiltration with lymphocytes, plasma cells, and leukocytes, formation of epithelioid cells and occasional giant cells, slight proliferation of fibroblasts, dilatation of blood vessels, and thickening of the intima of the blood vessels.

In the macule of syphilitic roseola the histologic changes are in a focal region of the skin and are slight. The papule represents an advanced lesion with extensive infiltration into the dermis just beneath the basal layer, with decreasing intensity in the deeper layers. The plasma cells are extremely conspicuous, especially in the later stages. The characteristic

copper color results from the large number of plasma cells, the increase in chromatophores and pigment, and the hemorrhage. The elastic fibers of the dermis become fragmented and disappear. The larger raised papules show in addition moderate acanthosis with a widening and elongation of the rete. In the papulosquamous variety there are acanthosis, edema of the epidermis, and hyperkeratinization with retention of the scales (Fig. 165).

retia grow irregularly and fuse with one another to form an intricate network. There are edema of the epidermis and infiltration of leukocytes with the formation of small pustules. Superficial ulceration is common. Infiltration of the dermis is predominantly with plasma cells, with only a few lymphocytes and leukocytes. There is proliferation of fibroblasts and budding of the capillaries in the dermis between the rete.

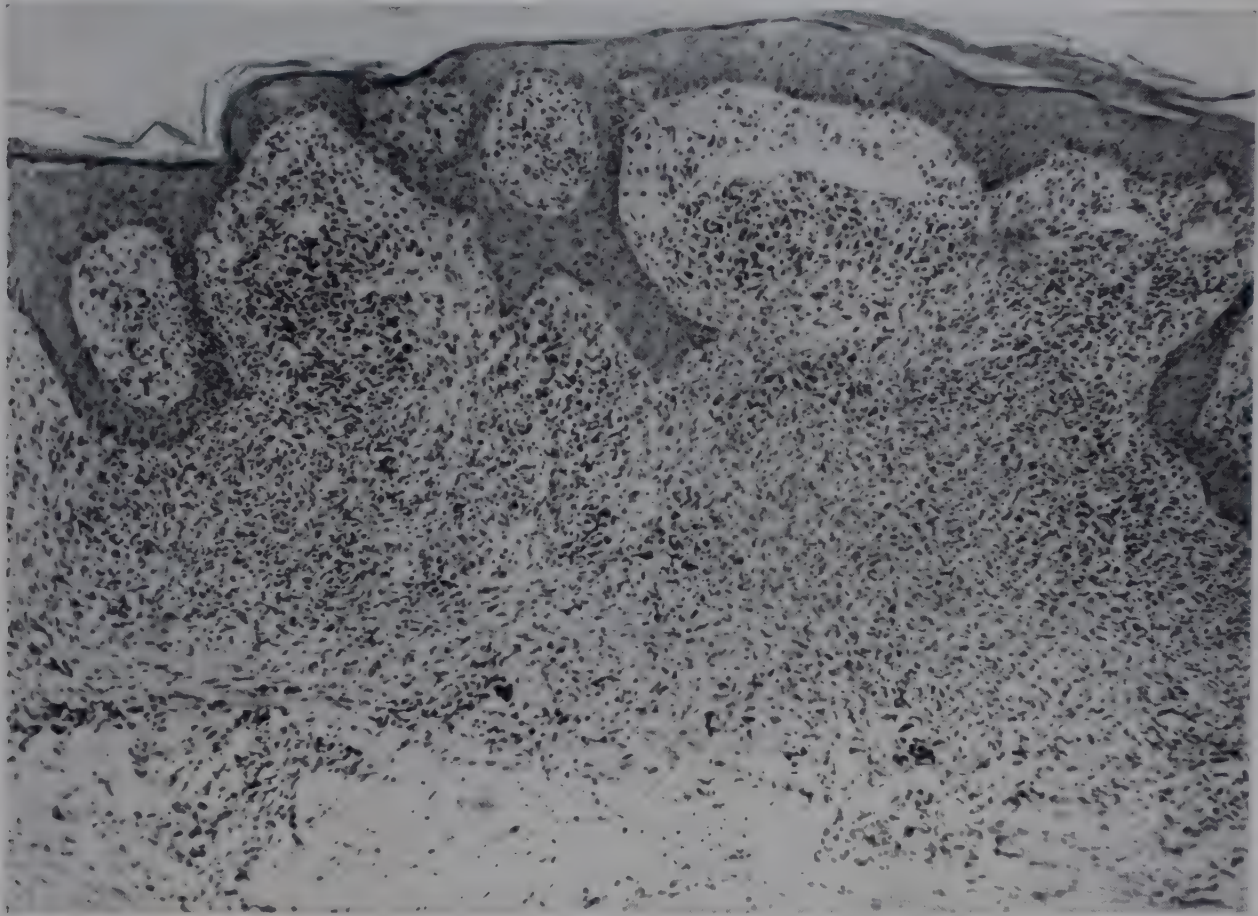


Fig. 165. Secondary syphilis (papulosquamous eruption). In the dermis there is a massive infiltrate made up of lymphocytes, plasma cells, and fibroblasts. The lymph spaces are dilated. Changes in the epidermis are secondary. (Photograph by courtesy of Dr. Zola Cooper.)

In the pustular varieties, fluid and leukocytes collect within the epithelium. The crustaceous type represents the collection and drying on the surface of a fibrinoserous exudate. As the inflammation continues, there is necrosis of the epidermis and the ulcer of syphilitic rupia results.

The vegetative lesions are represented by two types: the frambesiform syphilid and condyloma latum. The former is a red, finely nodulated, wart-like papule on the skin of the face and scalp. There are hyperplasia of the epidermis, elongation of the rete, and the usual infiltration into the dermis. Condyloma latum occurs on the moist, warm parts of the body. The lesions vary from a few millimeters to several centimeters in diameter. There is a tremendous acanthosis, and the elongated

The miliary papular syphilid is located about the hair follicles. There is a dense infiltration with lymphocytes, plasma cells, and a few giant cells. In the epidermis there are acanthosis and slight infiltration of cells. Syphilitic erythema nodosum is a focal thrombophlebitis with surrounding infiltration, gummatous necrosis, and proliferation of connective tissue.

Melanoleukoderma occurs as round or elongated unpigmented spots, up to a centimeter in diameter, with hyperpigmentation of the immediately surrounding zone. There are no chromatophores and no pigment in the basal layer in either ordinary preparations or in those stained by the dopa reaction. The arteries of the dermis are thickened and there is slight perivascular infiltration.

The alopecia of the scalp in syphilis may occur focally or as a general thinning of the hair. Microscopically an intense infiltration with plasma cells and lymphocytes about and into the hair follicles is observed. The blood vessels about the follicles are thickened. As

formation of numerous giant cells and small granulomas (Fig. 166).

Bone. The rare examples of pain in the bones in early syphilis are probably related to a proliferative periostitis and destructive osteitis (Reynolds and Wassermann).

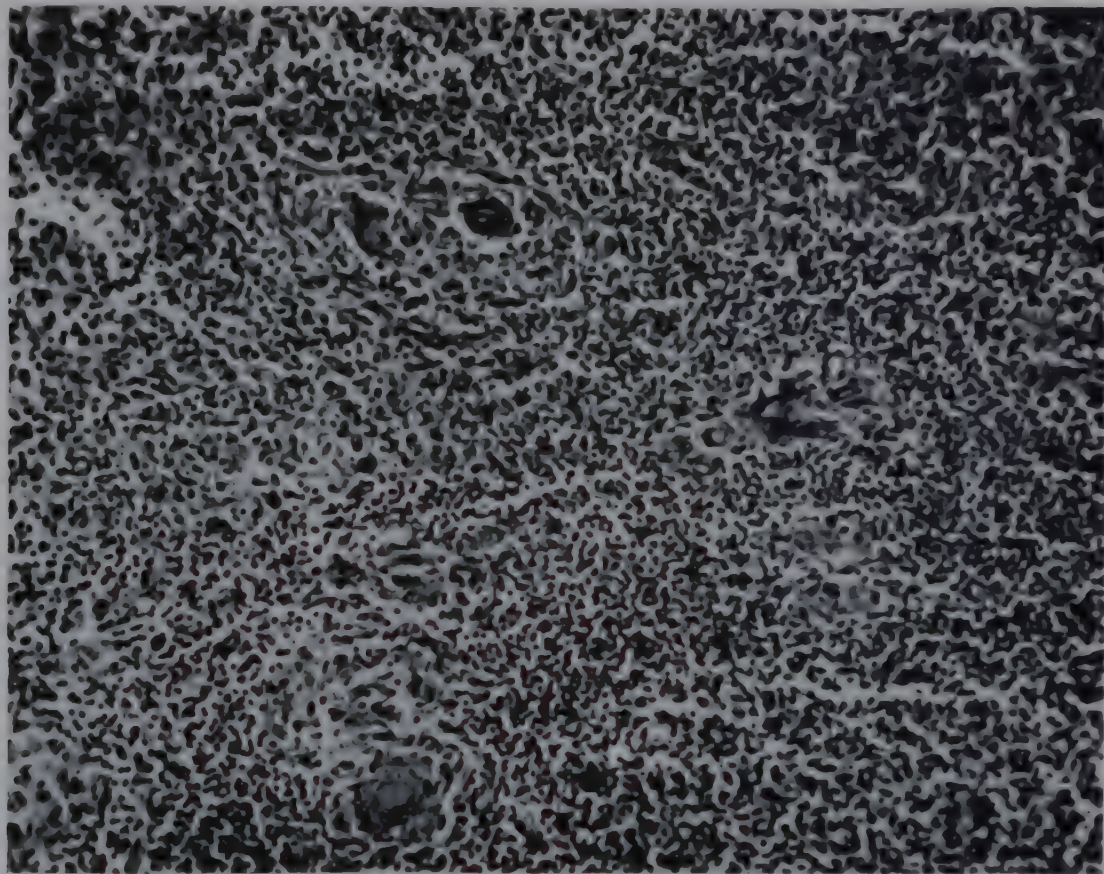


Fig. 166. Lymph node in secondary syphilis. From a young man who was accidentally killed within three weeks of the appearance of a chancre. (Tissue by courtesy of Captain Wilson Brown, A.U.S.)

a consequence of both of these processes, the follicles are in part or wholly destroyed. Paronychia in syphilis is not a histologic entity but only a localization of any of the above lesions of the skin in the tissues about the nails.

Lymph Nodes. In the late primary stage the lymph nodes generally become slightly enlarged, and firm. The follicular architecture is partially obscured by reticular hyperplasia and

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XL

Acquired Syphilis: Late Manifestations in the Cardiovascular System

Syphilis of the cardiovascular system is for practical purposes syphilis of the aorta and of the aortic valve. About 80 per cent of all syphilitic patients have grossly or microscopically demonstrable disease of the aorta. Of these, about 80 per cent again will have shown during life a positive Wassermann test (Beckh). Of all examples of syphilitic aortitis, about 20 per cent are clinically latent. About 25 per cent of patients develop an aneurysm, about 20 per cent have partial or complete occlusion of the orifices of the coronary arteries, and about 45 per cent have some evidence of involvement of the aortic valve. The average time period between the chancre and the development of symptoms resulting from syphilitic disease of the cardiovascular system is twenty years, although intervals as short as six months have been reported. So-called "syphilitic heart disease" constitutes about 5 per cent of all heart disease in white persons and about 30 per cent of all heart disease in Negroes.

Pathologic Anatomy. The pathologic anatomy will be discussed under five titles: "uncomplicated syphilitic aortitis," "aneurysms of the major arteries," "stenosis of the ostia of the coronary arteries," "syphilitic aortic valvulitis," and "syphilis of the myocardium." With the possible exception of the last, each of these represents not only a pathologic lesion but a clinical entity.

Uncomplicated Syphilitic Aortitis

By "uncomplicated" is meant the absence of the other four lesions associated with syphilis of the aorta and heart—in other words, there is no aneurysm, no stenosis, and no valvulitis.

Pathologic Anatomy. Distributed through-

out the aorta, but more particularly in the ascending aorta, there are elevated, gray or bluish translucent plaques. The surface of these plaques is irregularly furrowed and wrinkled, and the furrow and wrinkle follow the long axis of the vessel. On section the normally yellow media appears pale and unusually thin, and throughout it there may be small red dots and lines, representing the more acute lesions with rich vascularization. The adventitia is fibrotic and dense. The lesion rarely extends proximal to the upper limit of the sinuses of Valsalva, and the distal extent is frequently distinct, and is represented by a sharp line, rarely below the level of the diaphragm. The aorta as a whole is dilated and the circumference may exceed the normal by from 50 to 75 per cent. Microscopically two types of lesions are seen, acute and chronic. The acute lesions are areas of gummatous necrosis, usually in the adventitia, rarely in the media, surrounded by epithelioid cells and giant cells. The chronic lesions are thickening of the vasa vasorum, perivascular infiltration with lymphocytes and plasma cells, and fibrous replacement of the media. This last is particularly well shown in elastic tissue stains, with large areas completely devoid of muscle and elastic tissue.

Pathogenesis. The reason for the selective involvement of the thoracic aorta, and especially the ascending thoracic aorta, is probably that the thoracic aorta is more abundantly supplied with both vasa vasorum and lymphatics than is the abdominal aorta, and that syphilitic infection reaches it through the blood and the lymph (Klotz). The mechanism by which the media is replaced by fibrous tissue is not clear. The destruction may result from direct action of the spirochete, or may be in the nature of ischemic necrosis, induced

by the thickening and at times occlusion of the vasa vasorum.

Clinicopathologic Correlation. A considerable percentage of persons with uncomplicated syphilitic aortitis have no signs or symp-

elastica of the media. There is no hypertrophy and dilatation of the heart in response to uncomplicated syphilitic aortitis.

Syphilis of the Major Arteries Other Than the Aorta. Grossly demonstrable syphilitic dis-

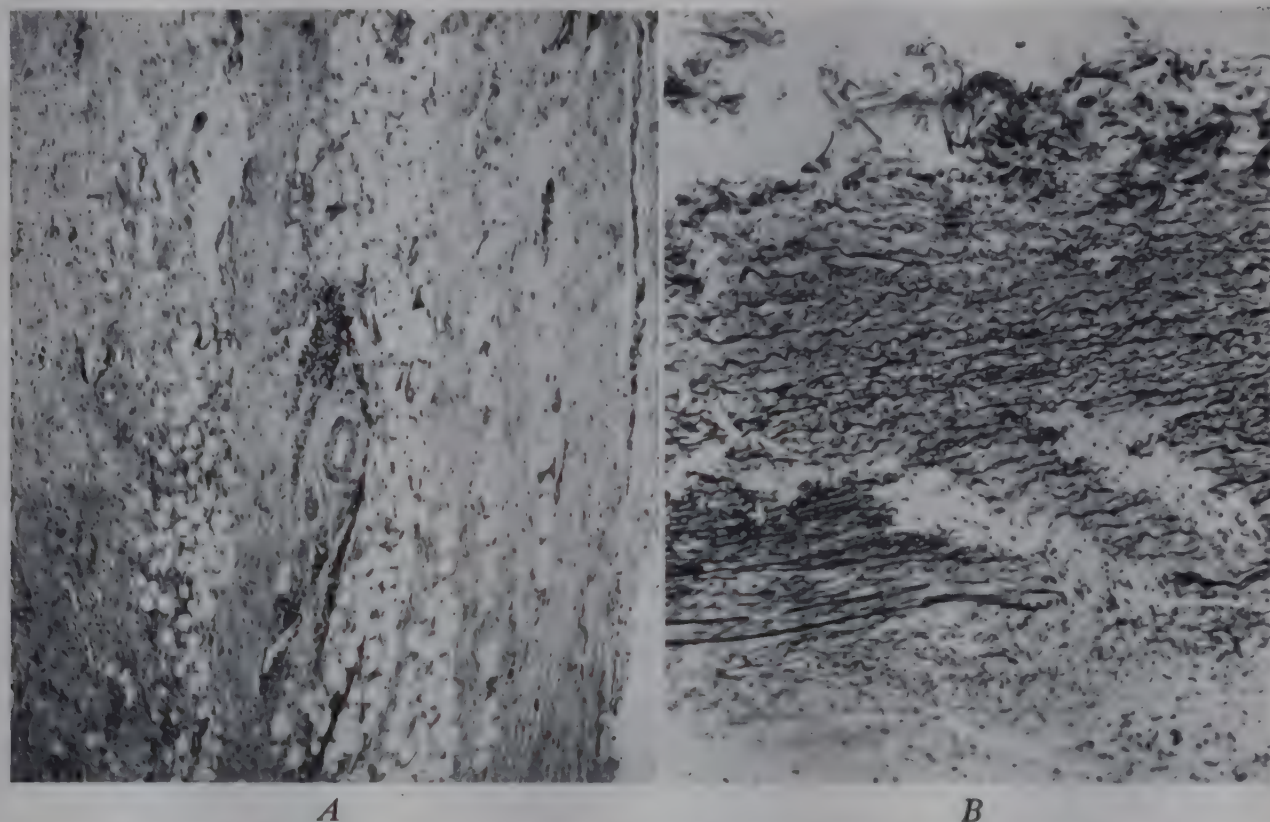


Fig. 167. Syphilitic aortitis. *A*, Fibrosis, endarteritis, and perivascular infiltration in the adventitia. *B*, Interruption of elastic lamina in the media.

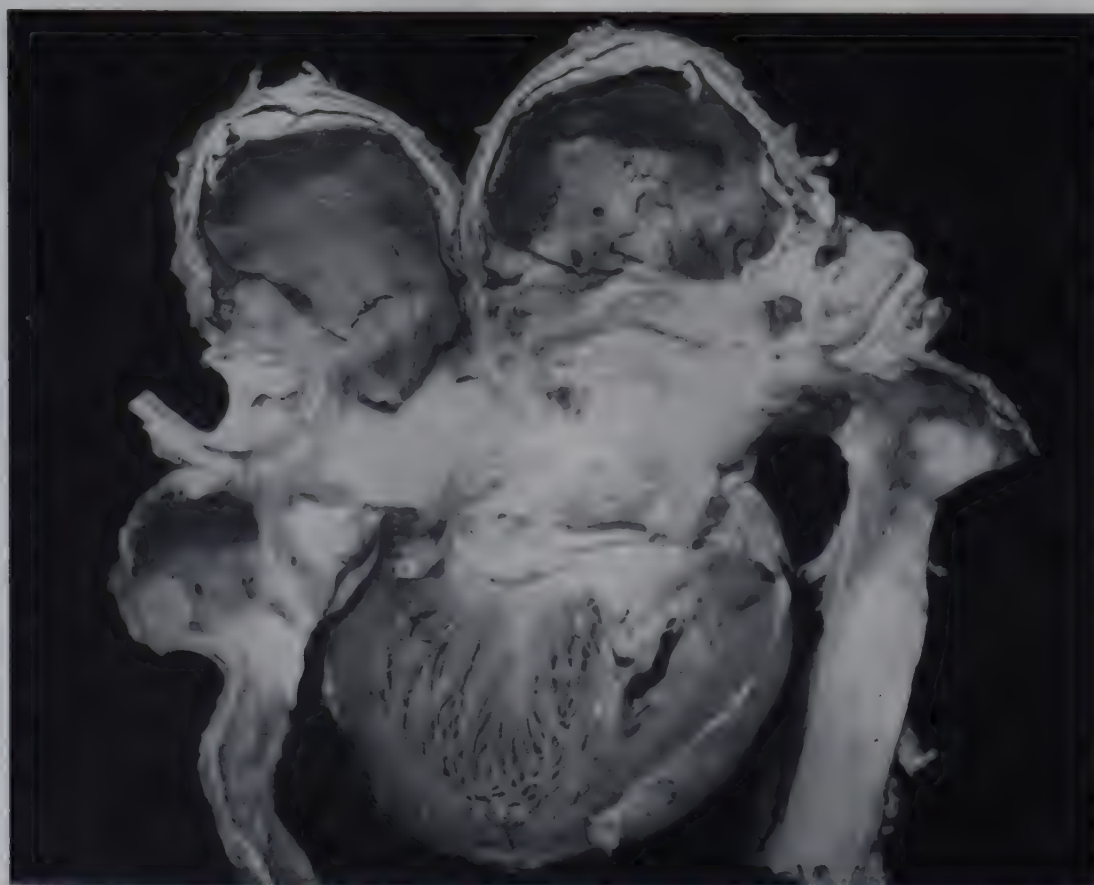


Fig. 168. Syphilitic aortitis with aneurysm of arch of aorta.

toms, and any correlation with the observed change in the first sound of the heart is difficult. The dilatation of the aorta, demonstrable by percussion or by x-ray, is closely correlated with the destruction of the muscle and

elastica of the media. There is no hypertrophy and dilatation of the heart in response to uncomplicated syphilitic aortitis. ease of the major branches of the aorta is unusual, but microscopic examination of the carotid, innominate, and coronary arteries frequently reveals definite change. In the latter arteries there is not infrequently an endar-

teritis, which contributes to the stenosis (Moritz).

Aneurysms of the Major Arteries

In the aorta and its branches, aneurysms related to syphilis or to arteriosclerosis are usually of the saccular or fusiform variety.

Incidence and Frequency. In general it may be said that aneurysms of the thoracic aorta are caused by syphilis and aneurysms of the other vessels may be caused by a variety of agents, of which syphilis is only one. The dis-

from 2 to 10 cm. in diameter and is usually sharply outlined. Microscopic examination at the orifice will reveal interruption of the media at the juncture of the wall of the aorta and the wall of the sac. The wall of the aorta shows all of the gross and microscopic changes of syphilitic aortitis. In the abdominal aorta saccular aneurysms are similar to those in the thoracic aorta; but the proof that one of these aneurysms is syphilitic in origin must rest upon definite demonstration of the typical histologic changes of syphilis. Fusiform and cylindrical aneurysms caused by syphilis represent noth-



Fig. 169. Laminogram showing a double aneurysm of the aorta. Note the line of calcification outlining the orifices and sacs of the aneurysms. (Radiograph by courtesy of Dr. Sherwood Moore.)

tribution of aneurysms of the aorta and its branches, taken from the analysis of 321 cases by Lucké and Rea, is as follows:

Thoracic aorta	238
Abdominal aorta	40
Innominate artery	13
Splenic artery	6
Renal artery	2

Pathologic Anatomy of Syphilitic Aneurysms. The typical saccular aneurysm of the thoracic aorta caused by syphilis is a mass varying from 5 to 25 cm. in diameter. The wall of the sac is composed of fibrous tissue with occasional muscle and elastic fibers. Within the fibrous tissue there are thickening of the vasa vasorum and perivascular lymphocytic infiltration. The mouth of the sac varies

ing more than extreme dilatation in a local segment of the vessel, and the appearance is similar to that in uncomplicated syphilitic aortitis.

Incidence and Causal Factors. In most general hospitals an aneurysm of the aorta is found in about one out of every hundred autopsies (Lucké and Rea). There is a preponderance in men of 8 to 2, and the average age is from thirty-five to fifty-five years, depending largely on when the syphilis was acquired. In the thoracic aorta, about 50 per cent of the aneurysms are in the ascending aorta, 35 per cent in the arch, and 15 per cent in the descending aorta (Boyd). The incidence in Negroes is greater than in whites, largely because of the greater incidence of

syphilis in the Negro, but possibly also related to the observation that aneurysms are more common in those who do hard physical labor.

Complications. Clinicopathologic Correlation. Aside from a few minor considerations, the clinical evidence for an aneurysm of the aorta is the presence of a space-consuming lesion within the thoracic cavity. As the aneurysmal sac increases in size it may press on the nerves, blood vessels, and the lumen of the respiratory or alimentary tracts, or on the solid structures that make up the wall of the

on the azygos vein may lead to right hydrothorax. Pressure on the innominate or subclavian arteries is detected by a difference in blood pressure and pulse in the two arms. These changes in hemodynamics may also be caused by incorporation of the orifice of the vessel in the aneurysmal sac and consequent loss of pressure and delay in transmission of the systolic thrusts of the heart in the easily expansible aneurysm. Pressure on the trachea and major bronchi is probably largely responsible for the frequent dyspnea, and ad-



Fig. 170. Kymogram showing the pulsation in an aortic aneurysm. (Radiograph by courtesy of Dr. Sherwood Moore.)

thorax. Pressure on the recurrent laryngeal nerve as it loops under the arch of the aorta results in the brassy cough and dysphonia. Pressure on the superior cervical sympathetic ganglia is probably responsible for the dilated pupil, widened ocular slit, and finally miosis and ptosis. The unilateral nature of the lesion leads to a difference in the size of the two pupils—*anisocoria*. Pressure on other blood vessels may involve the pulmonary artery, the major branches of the aorta, or the great veins as they enter the thorax through the superior mediastinum. This pressure on the superior vena cava will result in the syndrome typical of this condition: edema and cyanosis of the head, neck, and upper extremities. Pressure

hesions between the aneurysmal sac and the wall of the trachea bring about the typical tracheal tug. Pressure on the lumen of the alimentary tract leads to dysphagia. When an aneurysmal sac comes in contact with bone or other solid structures, it gradually erodes through them. The mechanism of the erosion is not clear. Erosion is best shown in the vertebral column where the bone is gradually destroyed, even to the extent of opening the spinal canal; while the cartilage of the intervertebral disks, being both elastic and avascular, shows no erosion. The characteristic bruit of an aneurysm probably results from the rush of blood through the orifice of the sac or from the eddying of blood within the sac. Aside

from all of the above clinical signs and symptoms, which vary from case to case, depending on the position of the aneurysm and the structures pressed upon, the most satisfactory diagnosis is based upon x-ray examination (Nichols, Ostrum, and Widmann). The paroxysmal nocturnal dyspnea present in about 25 per cent of instances is difficult to explain. It is present with syphilitic aneurysms, but rarely present in uncomplicated syphilitic aortitis (Keefer and Resnik).

Mechanism of Death. In general, persons with an aneurysm of the thoracic aorta die of rupture of the aneurysm, pressure on other organs and structures, or incidental causes (Kampmeier). About 35 per cent die of rupture, most commonly into the pericardium (Goldstein) or into the left pleural cavity. Ruptures into the right pleural cavity, into the trachea, into the esophagus, and into the left bronchus are next most common. Only about 5 per cent have the spectacular rupture through the thoracic wall (Lemann). Occasionally an aneurysm comes in contact with the superior vena cava, the pulmonary artery, or the right ventricle (Harris and Schattenberg), and an arteriovenous aneurysm is established between the two (Porter). The average life expectancy after a diagnosis of aneurysm of the aorta is two to three years.

Aneurysm of the Abdominal Aorta. These aneurysms are similar in their gross appearance to the saccular aneurysms of the thoracic aorta. They constitute from 10 to 15 per cent of all aneurysms of the aorta and are most common in that part of the aorta above the renal arteries. In most of them there is a laminated thrombus, partially or completely filling the sac (Kampmeier). Syphilis and arteriosclerosis are the more common causal agents. There are few signs or symptoms beyond the presence of a pulsating mass in the abdomen. About 70 per cent of patients die as the result of rupture into the retroperitoneal tissues (Lipschutz and Chodoff). If the aneurysm projects posteriorly there is the same erosion of the vertebra as in thoracic aneurysms.

Aneurysm of Other Arteries. Most aneurysms of the major branches of the aorta are caused by arteriosclerosis, trauma, or bacteria. Important arteries affected include coronary (Mitchell), renal (Lazarus and Marks), and splenic (Machemer and Fuge).

Stenosis of the Ostia of the Coronary Arteries

This lesion is present in about 20 per cent of all instances of syphilitic aortitis. The pearly gray plaques in the intima of the aorta project into and partially or completely occlude the orifices of the coronary arteries. In almost every instance of this condition the orifice of the coronary arteries is above the attachment of the aortic valves. The microscopic changes are typical of syphilis of the aorta (Von Glahn). An additional factor in bringing about stenosis is syphilitic endarteritis of the first portion of the coronary artery. In this condition there are the usual changes of arterial syphilis in the adventitia and the media of the first centimeter of the coronary arteries, but in addition there are thickening of the intima by granulation tissue, and severe reduction in the size of the lumen (Moritz).

Collateral Circulation. Thebesian Veins. The occlusion of the orifices of the coronary arteries in syphilis occurs gradually, and eventually, at least in some instances, no blood for the nourishment of the myocardium enters through the coronary system. This function is taken over by the normally inconspicuous thebesian veins that empty directly into the ventricles of the heart and anastomose through large and small openings within the coronary system (Wearn). In addition, there are the anastomoses of the atrial branches and pericardial branches of the coronary arteries with the internal mammary, anterior mediastinal, bronchial, phrenic, intercostal, and esophageal arteries. Under abnormal conditions these may dilate and serve as an adequate collateral circulation in occlusion of the coronary arteries (Hudson, Moritz, and Wearn).

Clinicopathologic Correlation. In most persons, again because of the slowness of the process, there are no signs of symptoms directly referable to the coronary arteries. Infarction practically never occurs, but sudden death is the rule.

Syphilitic Aortic Valvulitis—Aortic Insufficiency

These two designations, one anatomic and the other physiologic, are practically synonymous, since syphilitic aortic valvulitis almost invariably results in an aortic insufficiency,

and aortic insufficiency is rarely caused by any lesion other than syphilitic valvulitis. A few examples are dependent on chronic rheumatic disease of the aortic valve. There is fusion between the lateral part of the leaflets of the aortic valve and the aortic wall of the sinus of Valsalva. This leads to widening or

and retracted. In most instances there is intimal change in the aorta in the first 4 cm. above the valve, characterized by thickening, hyalinization, and longitudinal wrinkling. The heart is enlarged and may weigh as much as 1000 gm. The ventricular endocardium below the aortic valve is frequently thickened and



Fig. 171. Syphilitic aortitis and aortic valvulitis. (From the files of the Armed Forces Institute of Pathology.)

separation of the commissures at the point where the two leaflets insert. In the region of the commissure there are hyaline plaques of varying size, but the degree of separation is more dependent on fusion of the leaflet to the wall than on the size of the plaque. The valve leaflet, including the central part, is thickened

opaque, and small pockets may be found. The mouths of these pockets are directed toward the aortic orifice and it has been assumed that they represent an effect of the regurgitant stream of blood, and may be used as the anatomic evidence of aortic insufficiency. As most persons with aortic insufficiency die of

cardiac failure, all of the pathologic changes of chronic passive hyperemia are present in the viscera and in the extremities. Microscopically in the aorta there are the characteristic changes of syphilis. In the valve itself there are fibrosis, vascularization, and perivascular infiltration with lymphocytes and plasma cells.

Pathogenesis. It is difficult to evaluate the role of primary syphilitic inflammation and of ischemia in the production of the fibrosis of the valves. Careful histologic studies indicate that the initial changes depend on ischemia, and that in the later and more advanced changes the spirochete plays a direct role (Saphir and Scott).

Clinicopathologic Correlation. The essential changes are those of an insufficiency through the aortic valve (Scott). Subacute bacterial endocarditis on the basis of syphilitic aortic valvulitis is extremely rare (Koletsky).

Syphilis of Other Valves of the Heart. In spite of reports in the literature, there is no incontrovertible evidence that syphilis of the mitral and tricuspid valves ever occurs. In the rare cases of syphilis of the pulmonary artery it is possible that the pulmonic valve may be involved.

Syphilis of the Myocardium

The existence of and the pathologic criteria for the diagnosis of syphilis of the myocardium, other than the gumma, have been the subject of controversy for many years (Saphir). In congenital syphilis there are not infrequently many spirochetes in the myocardium, with or without acute or chronic inflammation. In acquired syphilis, chronic interstitial myocarditis, in which a few spirochetes can be demonstrated, has been reported, but this lesion is so frequently associated with arteriosclerosis of the coronary arteries that it cannot be conclusively attributed to syphilis. On the other hand, there is a definite lesion of the heart, termed acute syphilitic myocarditis. There are in the myocardium large, irregular, light yellow areas resembling infarcts. Microscopically the yellow areas are seen to be foci of necrosis of the myocardium, with a heavy infiltration of lymphocytes, polymorphonuclear leukocytes, and eosinophils. Stains for spirochetes show an enormous number in the lesions (Warthin).

Gumma of the heart is of little clinical significance unless it involves the bundle of His, with resultant complete heart block (Spain and Johannsen).

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XLI

Acquired Syphilis: Late Manifestations in the Nervous System

From 40 to 60 per cent of all persons who contract syphilis will within the first few months or years show some abnormality of the spinal fluid—positive Wassermann, pleocytosis, or increased globulin. There are no symptoms referable to the nervous system in most persons. With the lapse of years, especially if treatment is not adequate, an anatomic lesion of the brain or cord develops in a small percentage.

Familial Predisposition. The repeated observation of multiple cases of neurosyphilis in the same family, even when the disease is acquired from extra-familial sources, indicates that there may be a constitutional predisposition (Moore and Keidel).

Relation to Dermal and Osseous Syphilis. There is a general inverse ratio between the severity and the incidence of dermal and osseous syphilis and of neurosyphilis in any given person, possibly indicating some type of immunity or hypersensitivity (Shaw).

Importance of Neurosyphilis. Syphilis is the cause of the insanity in about 10 per cent of all persons admitted to hospitals for the mentally deranged in the United States. Approximately 3 per cent of all medical patients have neurosyphilis.

Anatomic Neurosyphilis. In 4880 autopsies at the Bellevue Hospital in New York, anatomic evidence of syphilis was found in 314, and syphilis of the nervous system in 105. This indicates that about one-third of all persons with syphilis have pathologic lesions of the meninges, brain, or cord (Symmers).

Although the anatomic varieties of neurosyphilis may be combined in any one patient, it is convenient to recognize six distinct types: paresis, tabes dorsalis, syphilitic leptomeningitis, syphilis of the cerebral arteries, syphilitic optic atrophy, and gumma of the brain. In the autopsies of any large general hospital, the

relative incidence of the lesions in all patients with neurosyphilis is about 20 per cent paresis, 20 per cent tabes, 30 per cent meningitis, 20 per cent vascular syphilis, and 2 per cent gumma of the brain (Marsh and Courville).

Miscellaneous Lesions of the Spinal Cord. Rare lesions caused by syphilis are: posterolateral meningomyelitis, Erb's disease—degeneration of the lateral white columns—syphilitic amyotrophic lateral sclerosis with changes similar to those in the agnogenic type, and a diffuse syphilitic myelitis (Adams and Merritt).

Syphilitic Meningitis

From a clinical standpoint there is perhaps no justification for the separation of syphilitic meningitis and cerebrovascular syphilis, as they are frequently associated in the form of meningovascular syphilis. But from the standpoint of pathology there is full justification for the division.

Pathologic Anatomy. In syphilitic meningitis the brain and cord are of the usual size. The dura mater is unusually adherent to the calvarium, and is slightly thickened. In the leptomeninges there are three distinctive types of lesions: opacity or turbidity, patches of fibrous thickening, and discrete focal lesions. The turbidity in the subarachnoidal space may be generalized or focal, and is most common over the hemispheres in the sylvian fissure, over the pons, in the interpeduncular space, and about the origin of the third nerve. The plaques of fibrous tissue are white or grayish white, and are most frequently seen in the meninges of the intercerebral fissure, varying from 1 to 10 mm. in diameter. They are firm, and rarely exceed 1 mm. in thickness. The focal lesions are found in sulci between the convolutions of the cerebral hemispheres, both

over the convexity and at the base. They are vaguely outlined, vary from 1 to 4 mm. in diameter, and occur singly or in groups. Throughout the leptomeninges there is a slight to moderate lymphocytic infiltration, especially about the smaller blood vessels. There is a similar infiltration into the spaces of Virchow-Robin in the peripheral parts of the cortex. There is also proliferation of the cells of the arachnoid with a variable amount of deposit of intercellular collagen. The discrete lesions are small gummas, or focal areas of lymphocytic infiltration (LeCount and

Cerebral Vascular Syphilis

The lesions in the large and medium-sized vessels are characteristic—Heubner's endarteritis. There is proliferation of the intima, usually eccentrically. The media and adventitia are infiltrated with a few lymphocytes and plasma cells. The muscle of the media may undergo necrosis, and be replaced by fibrous tissue. Secondary thrombosis and rupture of the vessel with extensive hemorrhage are not uncommon. Analogous changes occur in the veins. In the smaller arteries, there is a similar

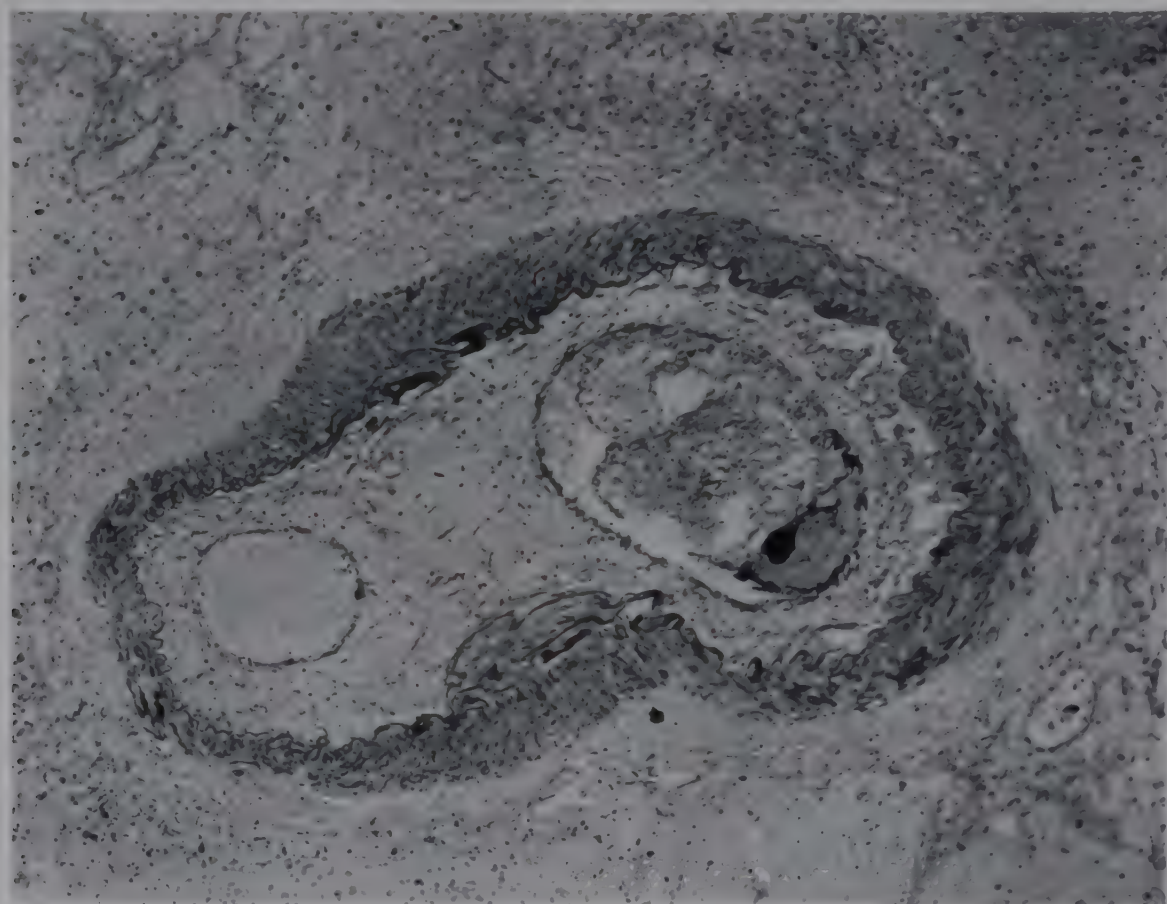


Fig. 172. Heubner's endarteritis in meningovascular syphilis.

Dewey). In rare cases, the lesions at the base are extensive and gummatous necrosis is prominent—chronic basilar gummatous meningitis.

In addition to the characteristic syphilitic leptomeningitis occurring in acute and chronic forms, the pathologist finds in autopsies on most syphilitics small foci of fibrosis and lymphocytic infiltration of the meninges (Warthin).

Pachymeningitis. In an occasional person with paresis there is a proliferative type of internal pachymeningitis with thickening of the dura. It is not proved whether this is the result of syphilis or a simple subdural hematoma caused by trauma.

change with partial or complete occlusion of the lumen (Rubinstein).

It is evident that the physiologic effect is to restrict the blood supply to the brain, both diffusely and focally. Focal ischemia results in hemiplegia, and other localizing signs and symptoms.

Gumma of the Brain

A gumma of the brain is a space-consuming focal lesion and gives many of the clinical signs and symptoms of a brain tumor. It is almost always solitary. All parts of the cerebral hemispheres are equally involved, except the occipital lobe, which is spared. The aver-

age size is 1 to 2 cm., and the gross and histologic picture is the same as that of gumma in other organs (Alpers).

Paresis

Paresis, dementia paralytica, or general paralysis of the insane, is frequently referred to as "parenchymatous" syphilis of the brain because of the involvement of the cerebral substance and of the ganglion cells. It is thus contrasted with "interstitial" syphilis, in which

gions, a granular ependymitis, and changes in the blood vessels.

The inflammation of the brain is characterized by an infiltration of plasma cells, lymphocytes, and mast cells in the perivascular spaces, and rarely into the cerebral substance. In the ganglion cells, there are all types of degeneration—loss of tigroid material, disruption of neurofibrillae, vacuolation, satellitosis, and neuronophagia. In the end, the cells are lost and there is a proliferation of fibrous glia in the region. In addition, a characteristic rod

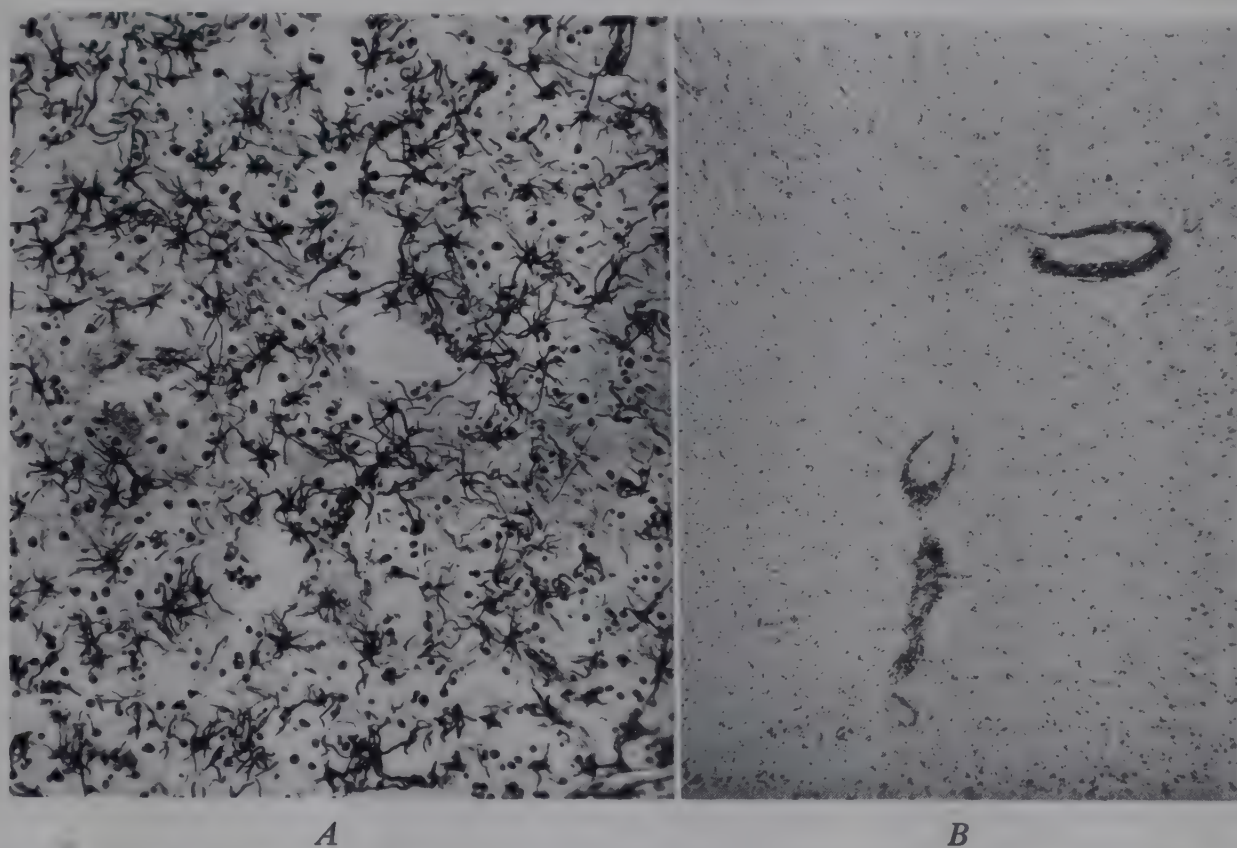


Fig. 173. Paresis. *A*, Giant glial cells in the motor cortex. *B*, Perivascular infiltration in the cortex.

the changes are in the glial cells and in the meninges.

Pathologic Anatomy. The brain is decreased in weight by 100 to 200 gm. The convolutions, except in the frontal lobes, are small, and the sulci are wide and deep. The leptomeninges are thickened and opaque. Because of the atrophy of the brain, there is an increase of fluid in the subarachnoid space and the ventricles are dilated. The ependymal lining of the ventricles is granular. In the spinal cord, the meninges are thickened and the lateral white columns are smaller than normal.

The changes seen microscopically in the cortex are: degeneration of the ganglion cells, inflammation and gliosis in the second and third cell layers of the cortex, storage of iron, loss of fibers radiating from the involved re-

cell, probably a hypertrophic microglial cell, is prominent, and a few gitter cells may be present.

The storage of iron is manifested by the presence of an iron-containing pigment free in the adventitia of vessels, in gitter cells, and oligodendroglial cells, and encrusted on the surface of ganglion cells. By chemical analysis, there is about twice as much iron as normal. The origin of the pigment is not known.

The loss of fibers in the subcortical white matter is first seen in the supraradiary and infraradiary systems, then in the tangential system, and finally in the projection fibers. In the latter instance, the pyramidal tract in the cord is lost. The loss of fibers and demyelination may be diffuse or focal.

The granular ependymitis is seen microscopically as a focal proliferation of the ep-

endyma and the subependymal glia. In the spinal cord, there is focal and diffuse infiltration of lymphocytes and plasma cells in the meninges and about the spinal roots.

Vascular changes include proliferative endarteritis in the smaller arterioles, and building of capillaries to form a richly anastomosing network (Hassin).

Special Types. Modification of the distribution, severity, and nature of the lesions is responsible for the special types of paresis.

Juvenile Paresis. This has already been discussed in the chapter on congenital syphilis (p. 312).

Lissauer's Type. The symptoms are those of a focal lesion and the pathologic changes are more conspicuous in the parietal and occipital lobes. There are outstanding degeneration of the ganglion cells and the formation of small gummas.

Stationary Types. Pathologic changes are inconspicuous and are limited to slight cellular infiltration into the meninges and the perivascular spaces and slight subpial gliosis.

Acute Paresis. Pathologic changes are most intense, and involve all parts of the brain and all cell layers of the cortex. Clinically, there may be delirium, convulsive seizures, catatonic phenomena, or an acute confusional state. Death may occur within a few days (Herman and Rosenblum).

Influence of Therapy. In persons treated by induction of malarial paroxysms, there is a period of six weeks in which the inflammatory reaction is intense, and the presence of the iron pigment is prominent. This is followed by a period up to three years in which there is some restoration of the normal structure. Spirochetes are not demonstrable after therapy (Wilson). The same general changes are observed after treatment with the arsenicals.

Incidence. The symptoms of paresis usually appear first between the ages of thirty and fifty, or five to fifteen years after the first infection. All races and all social groups are equally affected, but there is a preponderance in men in a ratio of 3 to 1.

Clinicopathologic Correlation. The correlation of the psychotic disturbances and the intellectual deterioration with the anatomic changes has not been adequately defined. However, certain signs and symptoms depend on organic lesions. The variable tremors are probably related to degeneration of the cere-

bellomesencephalic tract with loss of control over the pontine, bulbar, and spinal mechanisms. The dysarthria is ataxic, and ascribable to lesions of the olivocerebellar system. Loss of volitional control is associated with degeneration of the cells of Betz and of the pyramidal tract. Other motor phenomena, as apraxia and parakinesis, depend on loss of the cerebral association pathways. Focal signs and symptoms are probably caused by vascular spasm or miliary gummas.

The findings in the spinal fluid are relatively uniform: a positive Wassermann reaction, a pleocytosis of 25 to 50, an increase of protein and globulin, and a paretic colloidal gold curve (5554321000).

Tabes Dorsalis

Pathologic Anatomy. The pathologic changes in tabes dorsalis, or locomotor ataxia, are predominantly in the spinal cord and the attached nerves, but primary and secondary changes may occur in many other structures. The cord is usually small and the leptomeninges are thickened, gray, and opaque. The dorsal roots are distinctly smaller than the ventral roots. The brain in general shows no change, but there may be slight thickening of the leptomeninges at the base. On section of the cord the dorsal white columns appear gray, shrunken, and smaller than normal. Microscopically distinctive changes in the dorsal white columns, in the dorsal roots, in the leptomeninges, and in the dura mater are observed. In the dorsal columns there are, in the early stages, small discrete foci of demyelination and degeneration of axis cylinders. In the later stages these foci become confluent and the entire dorsal column contains few or no myelin sheaths and axis cylinders. There is proliferation of the fibrillary astrocytes and slight infiltration, especially perivascularly, with lymphocytes. There are similar changes in the tract of Lissauer at the sides of the dorsal horns.

The disease frequently involves the lumbar enlargement to a greater extent than any other part. Consequently in the lumbar region the area of degeneration of the dorsal columns is in the peripheral part of these columns, while in the cervical region the same degenerated fibers are in the center of the two dor-

sal columns—that is, in the column of Goll. It is only when the cervical region is involved that the column of Burdach shows degenerative changes. In the dorsal root, there are discrete or confluent foci of degeneration, especially well marked in the radicular nerve and at the point where the posterior root penetrates the arachnoid. In addition, there are an infiltration with lymphocytes and a proliferation of astrocytes, resulting in a small, firm nerve. In the leptomeninges there is infiltration

been advanced to explain the pathogenesis of the tabetic lesions, but none is entirely satisfactory. The earliest theory postulated that some toxin of the spirochete circulated in the cerebrospinal fluid, and because of tissue susceptibility induced degenerative changes in the dorsal roots and columns. With more precise knowledge of histopathology the theory of a primary lesion resulting from the direct presence of the spirochete in the radicular nerve or at the point where the nerve passes

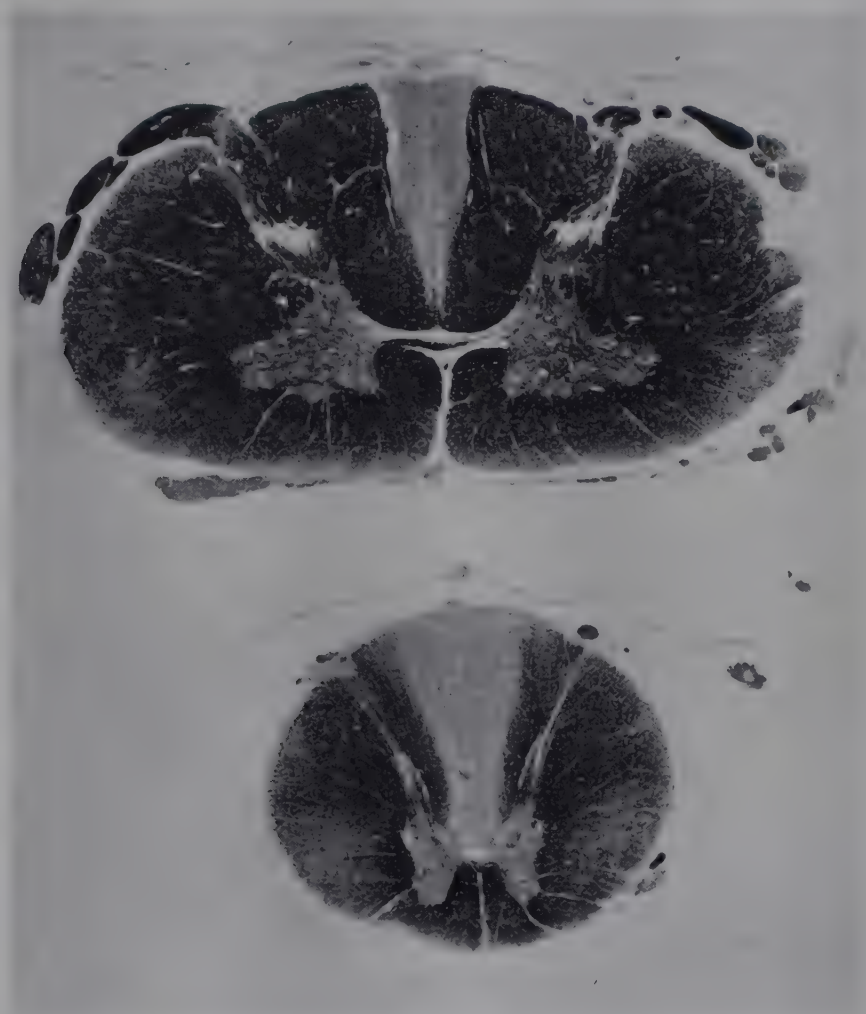


Fig. 174. Tabes dorsalis at two levels of the cord—dorsal and cervical.

with lymphocytes and proliferation of the arachnoidal cells, eventually leading to fibrosis. In the dura mater, especially in that portion immediately adjacent to the bone, there is a similar proliferation of fibroblasts and infiltration with lymphocytes. The peripheral nerves supplied from the involved dorsal roots show degeneration of the myelin sheaths and eventual loss of the axons. Changes similar to those in the dorsal spinal roots frequently occur in the sensory cranial nerves, particularly in the fifth nerve (Hassin; Stern). Occasionally there is some degeneration of the lateral columns of the spinal cord, suggesting combined system disease (Davison and Kelman).

Pathogenesis. Numerous theories have

into the arachnoid was advanced. Inflammation of the radicular nerve was thought to bring about degeneration of the fibers directly, while inflammation of the meninges at the point of entrance of the posterior root (area of Obersteiner-Redlich) was believed to press on the nerve fibers and cause degeneration. In both mechanisms the changes in the posterior column are assumed to be secondary. The third theory places the primary lesion in the arachnoid and in the epidural tissues. Inflammation at this point would obstruct the proper flow of cerebrospinal fluid, and the stasis in the subarachnoid space is assumed to induce degeneration in the posterior roots and columns (Hassin, Stern).

Incidence. Tabes dorsalis develops on an

average of seventeen years after the primary lesion, and is seen in men more frequently than in women in a ratio of 5 to 1.

Clinicopathologic Correlation. The loss of the peripheral and central processes of the cells in the dorsal ganglia involves a loss of the fibers mediating somatic sensation and proprioceptive sense, resulting in anesthesia or analgesia in the involved regions, and inability to stand perfectly erect with eyes closed (Romberg's sign). The loss of these fibers also interrupts the afferent part of many reflex arcs, so that there are a hypertonus and at times an atrophy of muscle. All of the deep reflexes are abolished for the same reason. In addition to these signs and symptoms resulting directly from the loss of nerve fibers and cells, there are a number of special features in tabes dorsalis.

Argyll Robertson Pupil. The typical Argyll Robertson pupil is small, constant in size, unaltered in size by light or shade, contracting fully and promptly on convergence, dilating when convergence is relaxed, and dilating slowly and imperfectly to mydriatics (Adie). The responsible lesion is a basal meningitis and interruption of the superficially placed fibers of the pupillomotor pathways as they pass from the posterior part of the optic tract to the anterior quadrigeminal bodies (Ingvar).

Tabetic Arthropathy, Charcot's Joint. The clinical and pathologic entity known as Charcot's joint is seen in a variety of diseases, notably tabes, syringomyelia, traumatic lesions of the spinal cord, leprosy, and lesions involving interruption of certain peripheral nerves to the extremities (Soto-Hall and Haldeman). The joint is swollen, the ligaments are elongated, and the synovial cavity is enlarged. Within the cavity there are small and large fragments of cartilage and bone. The articular cartilage is in part eroded and the trabeculae in the ends of the long bones are large, or fused together to form eburnated bone. In the shaft there is usually an osteoporosis. Microscopically no evidence of inflammation is observed but only destruction of cartilage and new formation of periosteal and periarticular bone (Moritz; Potts). Charcot's joint is the result of single or continued traumatism to a joint in which there is no sensory innervation (Eloesser). A person, following a fracture of a joint, may continue to walk on this joint because of the lack of pain. Within a few

months or a year he has developed the typical picture of Charcot's joint. It follows that any lesion, of which tabes is only one, that interrupts the sensory pathways to the large joints may be a contributing factor, but not the direct causal agent.

Blindness. Failing vision or blindness in tabes is most frequently related to primary optic atrophy, which is discussed later.

Crises and Lightning Pains. One of the most characteristic symptoms, and frequently the earliest, in tabes is the presence of transient burning or knifelike pains in the extremities. These are the result of the inflammation and early degeneration in the sensory fibers of the dorsal roots. Somewhat similar phenomena in the abdomen are known as crises. There is extreme pain and at times a constricting sensation about the upper abdomen. It is believed that these result from degeneration and inflammation in the sensory fibers of the tenth nerve, or in the myelinated sympathetic fibers in the dorsal roots.

Difficulty in Micturition. In over one-half of persons with tabes, there is difficulty in micturition, specifically hesitancy, feebleness of stream, incontinence, and retention. An exactly similar clinical condition can be produced in cats by section of the sacral dorsal roots. The tabetic lesion is the equivalent of section. The result is a loss of tone in the vesical musculature and a loss of the stretch reflex, so that the bladder continues to distend with urine, but does not empty itself except weakly or by overflow, and then incompletely. The retained urine frequently becomes infected and cystitis, ureteritis, and pyelonephritis follow (Emmett and Beare).

Perforating Ulcers. The initial lesion in perforating ulcers is an area of hyperkeratosis on the skin of the foot. This area then softens and the ulcer gradually erodes into the tissues and bone, until it penetrates to the opposite surface of the foot. The explanation is similar to that in Charcot's joint: continued trauma in a person who has lost the sense of pain. Secondary infection is also important in establishing chronicity.

Adie's Syndrome. This is a condition of unknown cause characterized by a tonic state of the pupil and a loss of one or more of the deep reflexes. It has some similarity to tabes, but is apparently not caused by syphilis (Dynes).

Syphilitic Optic Atrophy

Atrophy of the optic nerve may result from any of a variety of syphilitic lesions. The more important of these are disease of the retina and loss of ganglion cells, gummas or periostitis of the orbit with pressure on the nerve, and secondary invasion of the nerve by basilar syphilitic leptomeningitis; or it may be primary. In primary atrophy the initial change is degeneration of the marginal fibers in the intracranial part of the optic nerve distal to the chiasm. There are an infiltration with lymphocytes and plasma cells and proliferation of astrocytes. Spirochetes may be present, but there is no relation between the spirochetes or the inflammatory process and the degeneration. Unless treated, primary optic atrophy inevitably leads to blindness in an average period of two to three years. It is estimated that there are 50,000 people in the United States at all times with syphilitic optic atrophy. It is present in from 10 to 15 per cent of all tabetics (Moore).

Types of Optic Atrophy. All forms of atrophy of the optic nerve may on the basis of cause and clinical appearance be divided into five types: primary atrophy, secondary atrophy as the result of inflammation of the bulb, atrophy based on retrobulbar neuritis, atrophy localized in the papillomacular bundle, and atrophy associated with papilledema (Woods and Dunn; Moore).

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XLII

Acquired Syphilis: Miscellaneous Lesions of Late Syphilis

Late syphilis of the cardiovascular system and of the central nervous system is largely responsible for the deaths directly attributable to syphilis. In the other viscera clinically and anatomically demonstrable lesions may occur as frequently, but do not often cause death.

Late Syphilis of the Skin. There are two distinctive lesions of tertiary syphilis of the skin: the tubercular syphilid and the gumma. The former is a minute papule, usually multiple, and arranged in a serpiginous, circinate, or segmented fashion. Microscopically, small nodules of giant cells, epithelioid cells, and lymphocytes are seen in the dermis. The epidermis over the nodules may show acanthosis, hyperkeratosis, or pustules. Ulceration is not uncommon. When completely healed there remains a pigmented atrophic area of the skin. The gumma of the skin has the same characteristics as gumma in other tissues and organs.

Most secondary syphilids heal and leave no demonstrable change in the skin, but in a few there is either atrophy or loss of pigmentation or both. This type of lesion is seen most frequently over the neck and shoulders as discrete, small, depigmented spots with epidermal atrophy—leukoderma colli. Sections stained by the dopa reaction show no melanoblasts in the involved region.

Late Syphilis of the Bones. The pathologic picture at any stage in acquired syphilitic lesions of the bones varies with the location of the inflammation in the bone, the type of inflammation, and the type of reaction in the bones. Thus, a composite description of syphilitic lesions of the bones might read as follows: the tibia is increased in size and bowed anteriorly because of excessive formation of new bone in the periosteum on this one side—the saber shin of late syphilis. The bone is generally increased in density but through the

spongiosa there are numerous ovoid foci of resorption of bone. In the periosteum there are fibrosis, infiltration with lymphocytes and plasma cells, and the formation of numerous irregularly arranged new trabeculae of bone. Within the inflammatory tissue there are small gummas. The bone marrow is largely replaced by a loose connective tissue, infiltrated with lymphocytes and plasma cells, and set through with small gummas. In the trabeculae of the spongiosa there are fresh, healing, and healed minute fractures. In any one patient one type of change may overshadow all others (Freund).

The radiographic appearance is characteristic but variable. In a significant number of patients there is a definite history of trauma immediately preceding the onset of symptoms. The inflammation and new bone formation in the periosteum are responsible for the two outstanding clinical findings: pain and tumefaction (Conway). Gummas of the vomer and hard palate are the bases for the “saddle nose” and the perforation of the palate. Other sites of localization, in addition to the tibia, vomer and hard palate, are the clavicle, sternum, cranial bones, and long bones of the extremities.

Late Syphilis of the Joints. Aside from the Charcot joint, there are other types of lesion believed to be caused by congenital or acquired syphilis. It is difficult to establish positively that arthritis with effusion may be syphilitic (Kling). A preponderance of mononuclear cells in the fluid of patients, a positive Wassermann on the blood or synovial fluid, response to specific therapy, and recovery of spirochetes from the synovial fluid are inferential evidences (Chesney, Kemp, and Baetjer).

Inflammation of the bursae is a rare lesion in syphilis. It is frequently referred to as

"luetetic bursopathy" of Verneuil. The pathologic change varies from a serous inflammation with distention of the bursal sac, to the formation of a gumma with ulceration onto the surface of the skin. Primary bursitis should be distinguished from secondary invasion from a contiguous lesion in the bones or joints.

Late Syphilis of the Gastro-Intestinal Tract.

Buccal Cavity. Lesions in the buccal cavity are common and constitute some of the im-

Stomach. The characteristic lesion is a thickening and inflammation of the pyloric part of the stomach. The mucosa is atrophic or ulcerated. The submucosa is infiltrated with lymphocytes and plasma cells, especially perivascularly. A proliferative endarteritis and periphlebitis are conspicuous. Occasionally, there is an ulcer similar to the peptic ulcer. Patients complain of severe gastric disturbances simulating carcinoma, and there is said

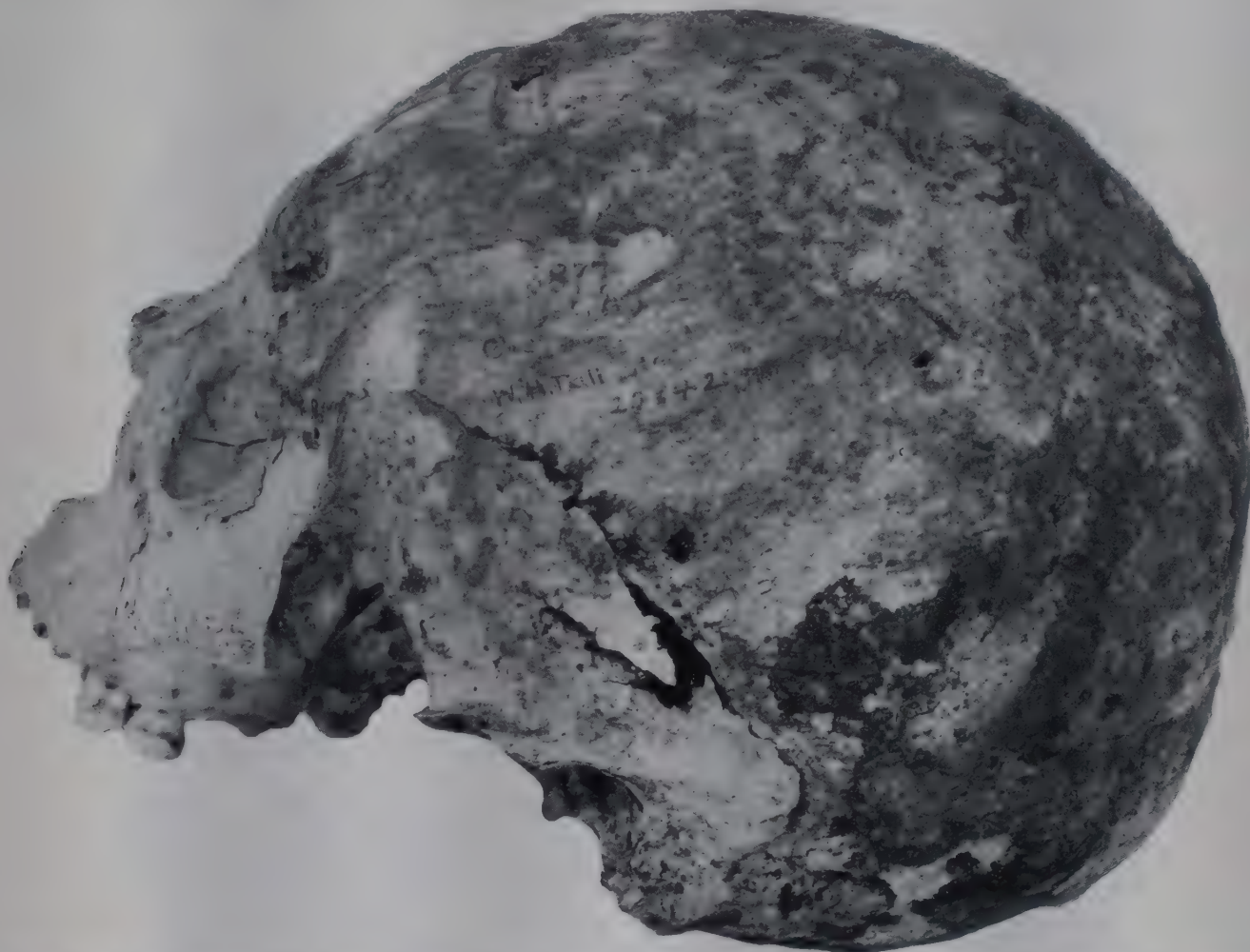


Fig. 175. Skull of an Aleutian Indian of early date said to show the lesions of syphilis. (Armed Forces Institute of Pathology, Neg. No. 67731.)

portant diagnostic criteria of late syphilis. The most frequently observed is a smooth atrophy of the base of the tongue. The mucous surface is smooth and devoid of lymph follicles. The underlying tissue is fibrotic and is infiltrated with lymphocytes and plasma cells. Another common manifestation in the mouth is syphilitic leukoplakia, which represents focal hyperplasia and keratinization of the epithelium. Gummas, especially of the hard or soft palate, with perforation into the nasal cavity occur. Less common are late nodulo-ulcerative syphilids of the mucous membrane. Chronic interstitial inflammation of the salivary glands is rare. Involvement of the esophagus is unusual, and is manifested as a fibrotic stenosing lesion (Kampmeier and Jones).

to be a typical radiographic appearance (Palmer).

Intestine. The rare lesions of the intestine occur in any part except the duodenum. They are multiple and annular, and may be either sharply punched out, clean, granulating ulcers, or gummas of the wall. In the rectum, the differentiation from venereal lymphopathy is difficult and it is probable that most cases of so-called "syphilitic stricture" of the rectum are really venereal lymphopathy.

Late Syphilis of the Respiratory Tract.

Nose. Gummas of the nose and hard palate have been mentioned as a late lesion in bone. Gummas of the palate may perforate and establish a fistula between the mouth and the nose.

Pharynx. Both gumma and diffuse inter-

stitial inflammation may occur in the pharyngeal mucosa and about the tonsils. In healing, there is extensive fibrosis with contraction and adhesions.

Larynx. The typical lesions in the larynx are single or multiple, submucosal nodules of chronic inflammation or gummatous necrosis with or without superficial ulceration, most commonly about the anterior commissure. In healing, there is extensive fibrosis. If the ulceration is deep, necrosis of cartilage and a perichondritis are present. The inflammation of the vocal cords is the cause of the usual symptoms of cough, hoarseness, and aphonia.

tion to form a large stellate scar. If these scars deform the liver in a manner to suggest lobulation, the term "hepar lobatum" is used (Fig. 176). The intervening parenchyma is prominent, and forms bulging masses of essentially normal hepatic tissue between the scars. Over the scars the capsule is thickened and adhesions to surrounding structures may be present.

In autopsy material, about 5 per cent of all persons with late syphilis show definite changes in the liver. Hepar lobatum produces significant clinical and functional changes in about one-quarter of patients. When signs

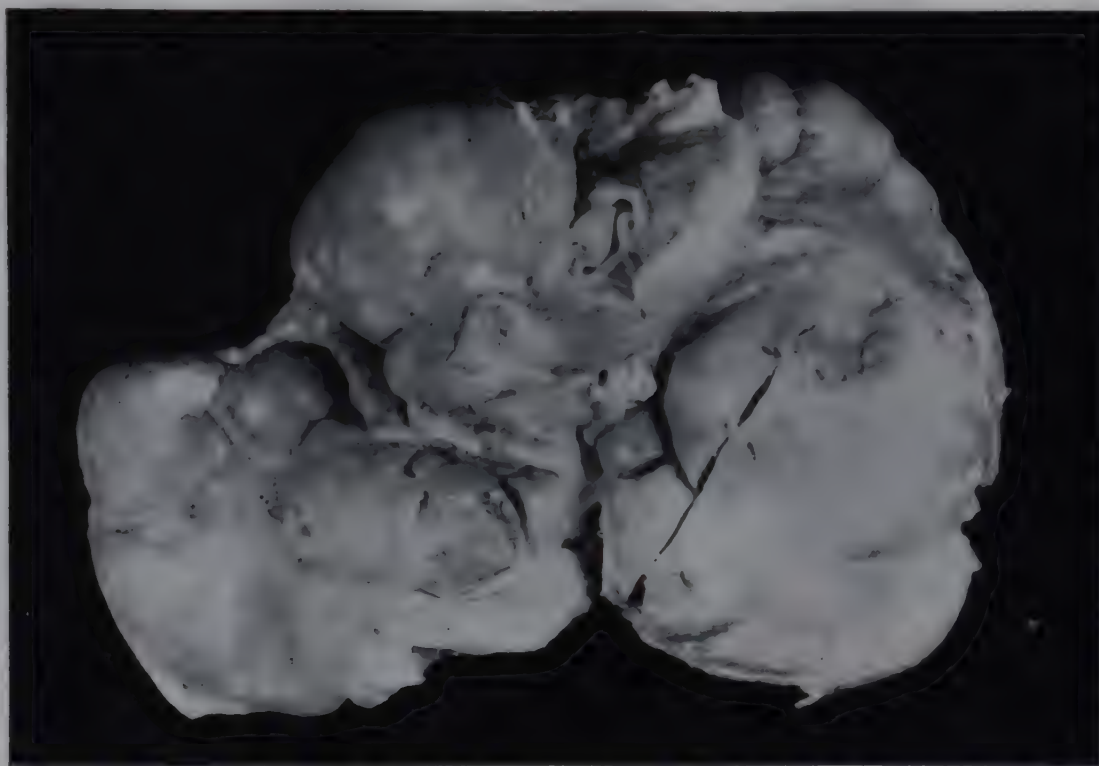


Fig. 176. Irregular lobulation of the liver in hepar lobatum.

Lungs and Bronchi. The only lesion of the lungs and bronchi which can be diagnosed with certainty as syphilitic is the gumma. It is rare and occurs as a single nodule 1 to 2 cm. in diameter in all parts of the lung. In many persons with syphilis, there is a diffuse or peritruncal fibrosis of the lung with infiltration of lymphocytes and plasma cells. Its relation to syphilis has not been established.

Late Syphilis of the Liver. The only lesion of the liver which can with certainty be diagnosed as a late manifestation of syphilis is the gumma, either a gummatous focus or the healed gumma—hepar lobatum.

The gumma of the liver has the same characteristics as the gummas of other organs. There are commonly 2 to 6 individual lesions, each 1 to 5 cm. in diameter, located in all parts of the liver or in one lobe. With healing there is extensive fibrosis and focal contrac-

are present they are usually those of portal or biliary obstruction—enlargement of the abdomen, ascites, bleeding from the intestine, and jaundice (Hahn).

Relation to Cirrhosis. Modern investigations do not support the concept of a diffuse syphilitic cirrhosis. There is conflicting evidence as to whether or not syphilis plays a secondary role in the causation of nodular cirrhosis. Most statistics show a slightly higher incidence of cirrhosis in persons with syphilis (Hahn, Shumacker).

Late Syphilis of the Pancreas. According to Warthin, many persons with syphilis have a chronic interstitial pancreatitis, characterized by a proliferation of a loose type of connective tissue, infiltration with lymphocytes and plasma cells, endarteritis, and loss of parenchyma. Aside from this slight change, syphilis of the pancreas is rare.

Relation to Diabetes. On the basis of clinical observation, diabetes mellitus does not occur more frequently in patients with syphilis than in the general population (McDaniel, Marks, and Joslin). Warren states that he has not seen a single pancreas from a diabetic in which he felt that syphilis caused the changes. Further studies are desirable.

Late Syphilis of the Urinary Tract. *Kidney.* Anatomic studies of syphilis of the kidney are not adequate. Rich has described a lesion present in about 6 per cent of persons with

Late Syphilis of the Genital Tract. *Testis.* There are two important and common manifestations of late syphilis in the testis: gumma and chronic interstitial inflammation. The typical gumma is solitary and is 1 to 2 cm. in diameter. From a clinical standpoint it is a space-consuming lesion. Chronic interstitial inflammation is observed frequently by the pathologist, but rarely causes clinical signs or symptoms. The tunica is thickened and opaque. Throughout all parts of the testis are interlacing, irregular foci of fibrous tissue, in-

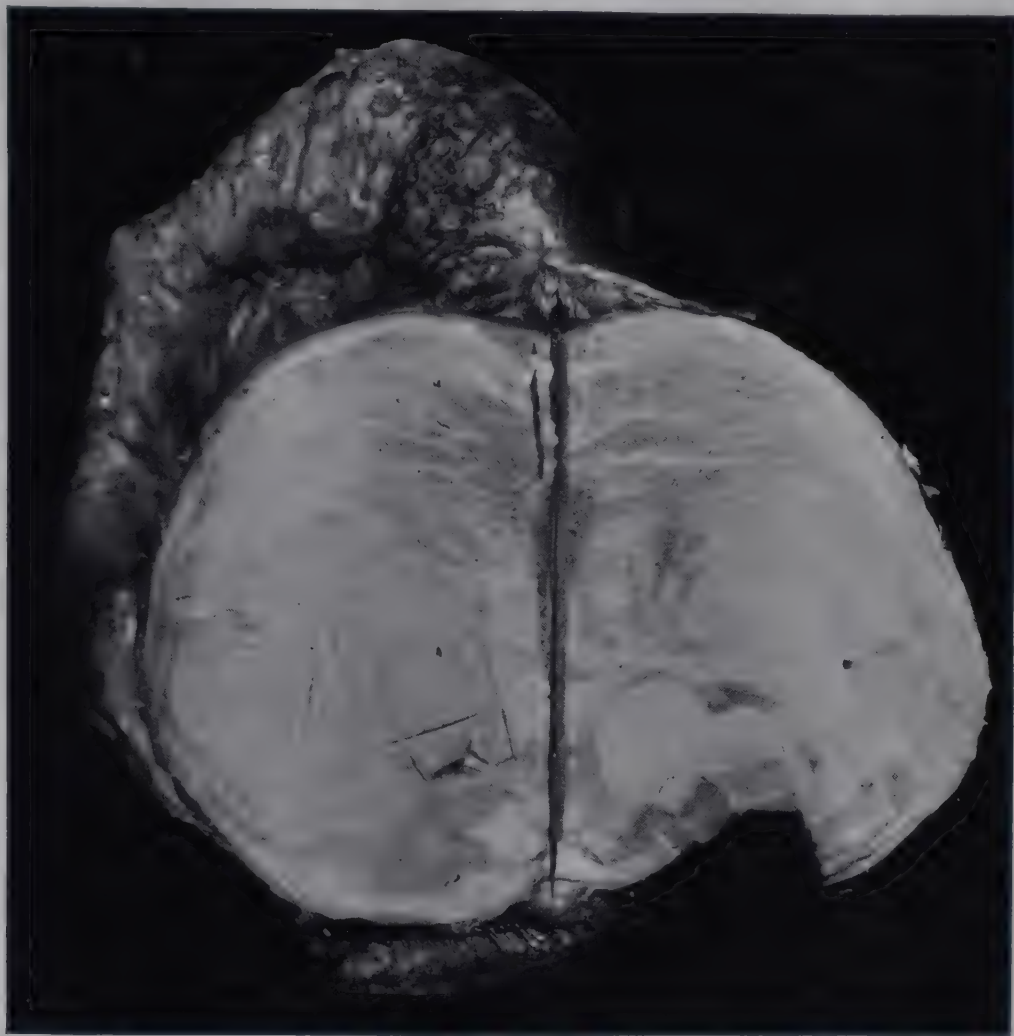


Fig. 177. Gumma of the testis.

syphilis which is not found in control material. Throughout the cortex are yellowish gray flecks, or multiple small scars formed by a focal infiltration of lymphocytes, mononuclear cells, plasma cells, and a few eosinophils, deposition of cholesterol, and fibrosis. The infiltration deforms the tubules and eventually destroys them. Spirochetes cannot be demonstrated. The clinical significance of the lesion is not established.

Bladder. Spirochetes have not been demonstrated in any reported late syphilitic lesion of the bladder.

The reported examples of late syphilis of the ureter and urethra are too indefinite to discuss.

filtrated with lymphocytes and plasma cells. The tubules cannot be picked from the cut surface, as in the normal state. The seminiferous tubules are atrophic. Spermatogenesis is depressed and the basement membrane of the tubule is thickened. The interstitial cells of the testis are decreased in number.

Other Genital Organs. Syphilitic lesions of the ovary and of both the male and female secondary sexual organs including the breast are extremely rare.

Late Syphilis of the Endocrine Glands. *Pituitary.* Lesions in the pituitary gland are occasionally observed, either small gummas or areas of fibrosis infiltrated with lymphocytes and plasma cells. If there is destruction

of the greater part of the anterior lobe, the patient may show diabetes insipidus, Fröhlich's syndrome, or hypophyseal cachexia (Kennedy and Fisher).

Thyroid. Both chronic interstitial inflammation and gummas of the thyroid have been described, usually in association with extensive syphilis of the larynx or trachea. The gland is moderately enlarged, and there is little functional alteration except in advanced lesions (Riecke).

Adrenals. Warthin ascribed small foci of lymphocytic infiltration in the cortex and perivascularly to syphilis.

Late Syphilis of the Eye. About 10 per cent of all blindness is caused by or is related to syphilis, mostly on the basis of the interstitial keratitis of congenital syphilis.

In acquired syphilis, ocular manifestations may appear in the secondary or tertiary stage. The most common lesions in order of frequency are iritis, kerato-iritis, neuroretinitis, iridocyclitis, and interstitial keratitis. In all there is perivascular or focal infiltration with lymphocytes and plasma cells, and eventually fibrosis. Miliary gummas occur (Igersheimer). In late syphilis iritis is more common in Negroes than in whites, and lesions first appear about ten years after the first infection (Moore).

Late Syphilis of the Ear. Lesions of the ear in acquired syphilis are rare. Both the vestibular and cochlear parts of the labyrinth may be affected bilaterally. There are thickening of the periosteum, fixation of the foot plate of the stapes, fibrosis and infiltration with lymphocytes and plasma cells of the organ of Corti and membranous canals, and diffuse fibrosis.

Deafness and vertigo may come on suddenly, presumably because of edema, or gradually because of fibrosis. Gummas of the petrous bone have been observed.

Amyloidosis in Late Syphilis. In an occasional patient with florid, untreated, late syphilis, especially of the bone, there is typical amyloidosis of the liver, spleen, and kidneys. In one example I have seen there was fibrosis of the kidney and death from uremia.

Lesions Caused by Arsenical Treatment. In about one of every 25,000 patients given intravenous injections of arsenicals for syphilis there is a fatality. The anatomic lesions in the

delayed type are of four types: acute yellow atrophy, hemorrhagic encephalitis, exfoliative dermatitis, and hypoplasia of the bone marrow (Hahn). All of these are described in other sections of this book except the hemorrhagic encephalitis. In this condition there are numerous small, discrete or confluent hemorrhages throughout the brain, especially in the mesencephalon. There is little or no inflammatory reaction (Scott and Moore). Most evidence indicates that all types are essentially arsenic poisoning caused by the liberation of trivalent, inorganic arsenic from the organic arsenical. The Herxheimer reaction is associated with a transient acute inflammation in the syphilitic lesions (Sheldon and Heyman).

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XLIII

Gonorrhea. Chancroid

There are two venereal diseases caused by bacteria: gonorrhea (*Neisseria gonorrhoeae*) and chancroid (*Hemophilus ducreyi*).

Gonorrhea

Gonorrhea is one of the bacterial diseases in which the ultimate proof of the causal relation of the bacterium to the disease has been submitted—reproduction of the lesions in man by inoculation of pure cultures (Finger, Ghon, and Schlagenhauser).

Pathogenesis and Influence of Epithelial Type. The injection of either killed cultures (Scholtz) or the alcohol precipitate of a fourteen-day broth culture—gonococcin (de Christmas)—into the human urethra provokes a transient purulent inflammation similar to that of clinical gonorrhea. In animals the nucleoprotein fraction of the cocci is as lethal as the living organism (Boor and Miller). From these and other observations it may be concluded that the gonococcus elaborates an endotoxin but not an exotoxin, and that the inflammatory reaction is largely a response to endotoxin liberated by autolysis of dead bacteria. Hence the incubation period of three to five days might be looked upon as the time required for the cocci to multiply and for some to die and liberate the irritating endotoxin.

In man inflammation of the genital tract depends on the epithelial type. In general surfaces covered by squamous epithelium are highly resistant, surfaces covered by columnar cells are highly susceptible, and surfaces covered by transitional cells vary. Those that are expansile are resistant and those that are not expansile are susceptible (Pelouze). Direct experimental proof of these conclusions is given by the observation that conversion of the transitional vaginal epithelium of young

girls (susceptible) to squamous epithelium (resistant) by injection of estrogen effects improvement of vulvovaginitis.

Acute Gonorrhea in the Male. Acute gonorrhea occurs in the urethra. After from three to five days, there is an acute purulent inflammation of the anterior urethra. The lumen is partially or completely filled with polymorphonuclear leukocytes and many cocci, largely intracellular. The epithelium is edematous and in regions may be partially desquamated. The connective tissue beneath the epithelium is edematous, hyperemic, and infiltrated with polymorphonuclear leukocytes. So far as can be determined the bacteria do not penetrate more than a few millimeters into the surrounding tissue. The glands and evaginations of the urethra show a similar pathologic change, with infiltration with leukocytes, and edema and hyperemia of the surrounding tissue.

Complications of Gonorrhea in the Male.
Prostatitis and Seminal Vesiculitis. In a certain percentage, less today than formerly, acute gonorrhea in man extends into the posterior urethra and involves the prostatic ducts and acini. There is the usual acute purulent inflammation, and in some instances formation of abscesses by destruction of the acinic and ductal walls and extension into the surrounding stroma. As in all examples of acute swelling of the prostate, there is severe pain, referred to the perineum. In the same cases or in others the infection extends to the seminal vesicles. In both prostatitis and seminal vesiculitis the inflammation may become chronic with replacement of the leukocytes by lymphocytes. Under these conditions bacteria are difficult to demonstrate in the tissues but may be recovered by cultural methods (Saigrajeff).

Urethral Stricture. In the event of ulceration of the urethra during the course of acute gonorrhea or as a consequence of instru-

mentation during treatment there is excessive proliferation of fibrous tissue and constriction of the lumen of the urethra in one or more regions, usually deep in the anterior urethra or the membranous urethra (Stone).

Epididymitis. Acute purulent epididymitis occurs during the second to fourth week of acute gonorrhea in men. The lumens of the tubules are filled with leukocytes, and there is excessive destruction of the epithelium and ulceration of the surrounding tissue (Campbell). With subsequent organization many of the tubules are obliterated and about 45 per

cent of patients who have had bilateral epididymitis have permanent aspermia and are sterile (Schmidt).

Septicemia. In an occasional patient a typical systemic infection may develop. It is characterized by a syndrome of profound illness, arthritis, and an erythematous macular eruption of the skin. Recovery is the rule. Histologic study of the skin shows necrosis of the arterioles and suppurative inflammation. Gonococci are present (Keil).

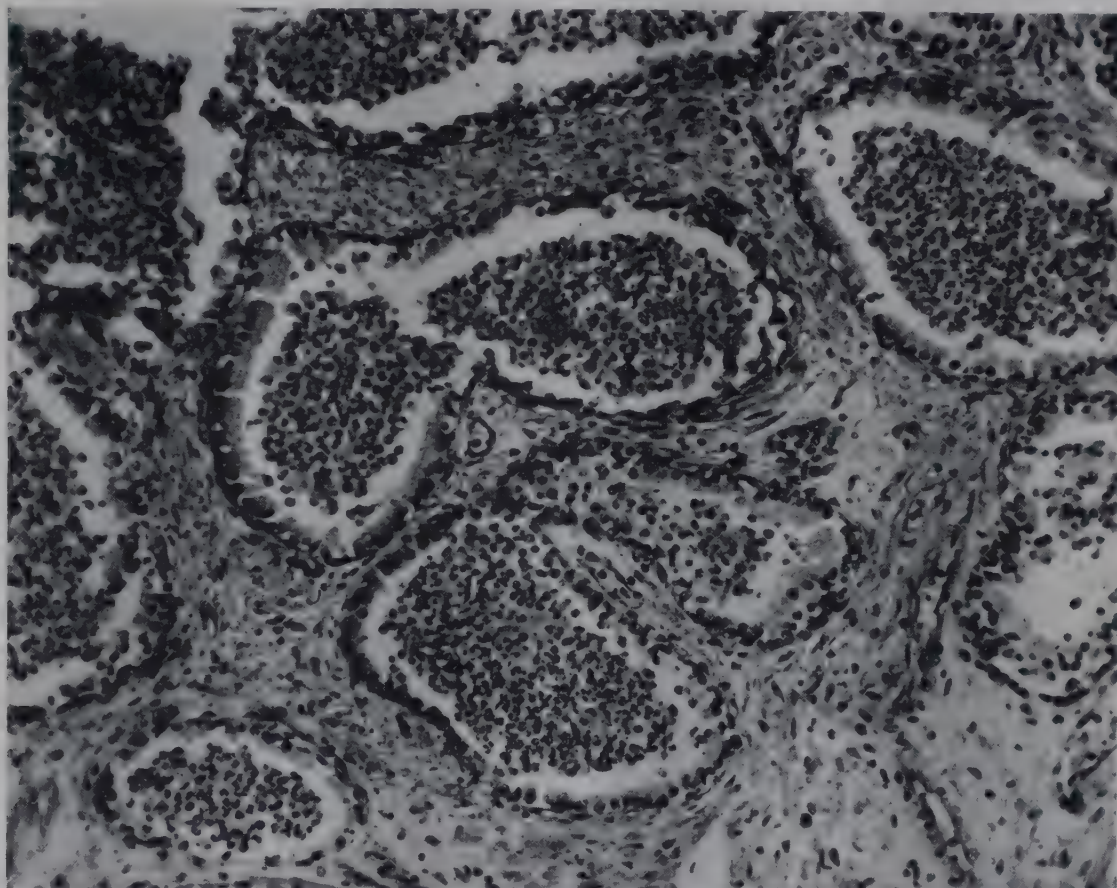


Fig. 178. Acute gonococcal prostatitis (from a case in the files of the New York Hospital).

cent of patients who have had bilateral epididymitis have permanent aspermia and are sterile (Schmidt).

Cystitis and Pyelitis. If the gonococcal inflammation involves the posterior urethra and prostate there is usually an associated inflammation of the vesical trigone, similar to that caused by many other bacteria. Less commonly there is a widespread cystitis and rarely the upper urinary tract becomes infected. The ureters are thickened and dilated, the kidney is enlarged, and the capsule is thickened and adherent. The pelvis is dilated and filled with thick pus, and there are numerous abscesses throughout the parenchyma. The dominant cell is the leukocyte (Parmenter, Foord, and Leutenegger).

Systemic Lesions. At any time during an

attack of acute gonorrhea, cocci may enter the blood and cause systemic or focal disease. The usual time of appearance of systemic lesions is four to eight weeks after the onset of the urethritis.

Endocarditis. In a small percentage of patients with acute gonorrheal urethritis a vegetative ulcerative endocarditis is initiated one to several weeks after the onset of the urethritis. The vegetations are typically large and friable, and are associated with extensive destruction of the valvular tissues. In about one-third of instances the vegetations are found on the atrial wall and on the chordae tendineae. The aortic valve is most frequently involved, but in contrast with most other bacterial endocarditides, over 10 per cent of examples of gonococcal endocarditis involve the right side of the heart.

Arthritis. Arthritis develops in about 2 per cent of persons with gonorrhea. There is a sexual preponderance of 2 to 1 in men. In early stages and in mild cases the inflamma-

tion is confined to the periarticular tissues. In severe forms there is inflammation of synovia, proliferation of tissue, and destruction of articular cartilage. Without adequate treatment, 25 per cent of the patients lose some function of the joint (Wehrbein).

TENOSYNOVITIS. Gonococcal tenosynovitis usually involves the flexor tendons of the hand. The sheath is filled with a thick translucent gray pus, in which organisms can be demonstrated (Hamlin and Sarris).

MENINGITIS. Acute gonococcal meningitis is extremely rare. The postmortem findings are similar to those in other types of bacterial

prominent. The cervix is red, and, dependent on the degree of edema, the cervical canal is turned outward and appears in the central part of the cervix. In all of the lesions there are infiltration with polymorphonuclear leukocytes, dilatation of the vessels, and edema of the tissues. Gonococci are readily demonstrated in the pus and in the superficial parts of the tissue. The vagina shows little change.

Complications of Gonorrhea in the Female. The important complications of gonorrhea in women are suppuration in the accessory glands, chronic cervicitis, and inflammation of the adnexa.



Fig. 179. Urethritis and Bartholin's glanditis. On retracting the labia, the external urinary meatus appears as a reddened elevated area. The mucosa is thickened and more or less everted. This is especially noticed in the labia of the urethra. The exit to Bartholin's gland on the right side is reddened, and presents the typical appearance of a gonococcal macula. A small drop of pus is seen to exude. As a result of the irritating discharge, the vulvar orifice is seen to be more or less inflamed. The infection of the crypts about the urethra is well illustrated. (Courtesy of Dr. C. C. Norris.)

meningitis (Strumia and Kohlhas). It is possible that the condition is frequently unrecognized—2 per cent of 500 cultures sent to the New York laboratories as meningococci were actually gonococci (Branham, Mitchell, and Brainin).

Acute Gonorrhea in the Female. Typical gonorrhea in women is an acute purulent inflammation of the labia, the urethra, and the cervix. The labia are swollen and red, and are covered in part by a purulent exudate. The mouths of the periurethral glands and of Bartholin's and Skene's glands are everted and dark red. Pus can be expressed from these orifices. The urethra is everted, swollen, and

Accessory Glands. The purulent inflammation in acute gonorrhea may extend into the deeper major glands about the labia—Skene's glands and Bartholin's glands. If drainage is inadequate, the entire gland undergoes suppuration and an abscess is formed. Exceptions must be recognized to the old dictum that an abscess of Bartholin's glands is invariably gonococcal in origin.

Chronic Cervicitis. Gonorrhea in the woman is a latent infection in the cervix. The initial eversion of the cervix persists and is fixed by the proliferation of fibrous tissue. Thus the central part of the cervix consists of a red, granulating surface, not covered by squamous

epithelium. There is dilatation of vessels and infiltration with lymphocytes and mononuclear cells. Many of the glands become occluded and small cysts form.

Lesions of the Adnexa. Pelvic Inflammatory Disease. About 70 per cent of all examples of salpingitis, both acute and chronic, are caused by the gonococcus. The remainder are associated with streptococci and staphylococci and tubercle bacilli.

PREDISPOSING FACTORS. The spread of gonorrhea to the tubes seems to be influenced by menstruation (the onset is frequently imme-

to one another. Thus in a characteristic chronic salpingitis the lumen is represented by numerous irregular isolated epithelium-lined spaces, and there is no open communication between the peritoneal cavity and the uterus. As a consequence chronic salpingitis is the most frequent cause of sterility in women, producing this condition by blocking the pathway of the ovum from the ovary to the uterus (Schwartz). It is also a predisposing factor in ectopic pregnancy, for the fertilized ovum may be trapped in one of the evaginations of the lumen and implant there.

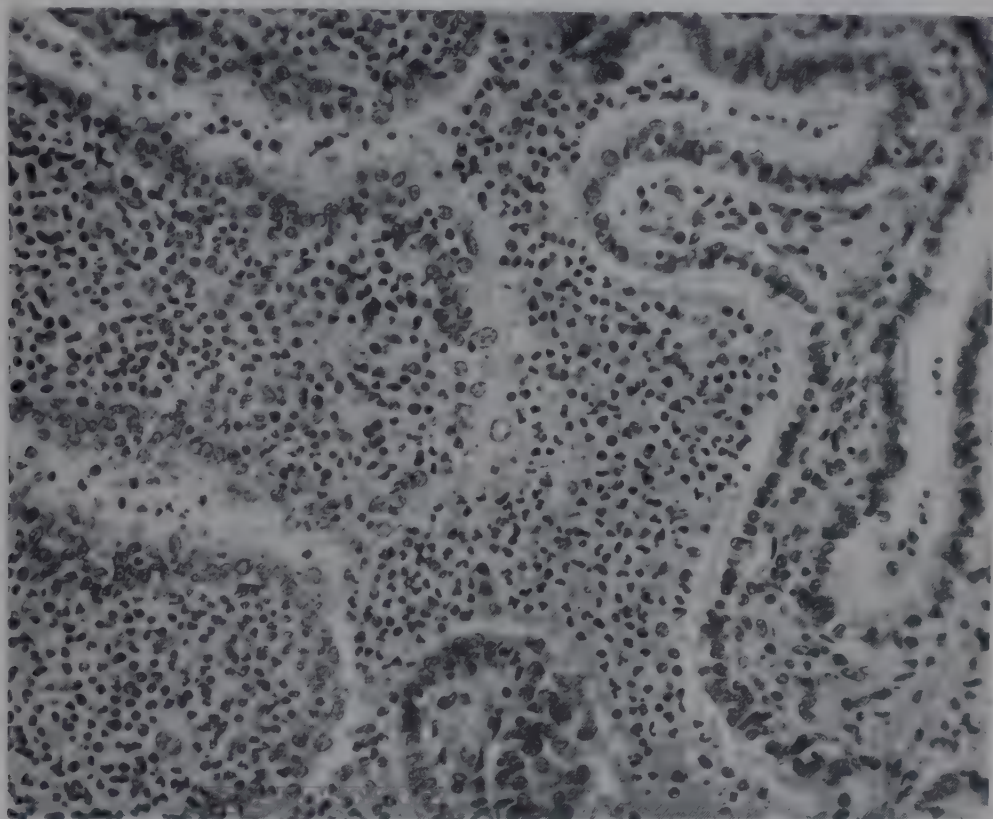


Fig. 180. Acute salpingitis.

diately after a period) and by dilatation of the cervix as in too vigorous treatment of acute gonorrhea, in surgical procedures, or during an abortion (Goodwin). These facts suggest that the gonococci pass along the mucosa rather than in the lymphatic vessels.

SALPINGITIS. The tube is red and swollen, and the fimbriae are prominent. From the open extremity pus may be expressed. The rugae of the mucous membrane are swollen, the blood vessels are dilated, and there is an intense infiltration of polymorphonuclear leukocytes both within the tissue in the epithelium, and in the lumen. As the inflammation subsides there is infiltration of mononuclear cells and plasma cells, and gradual disappearance of the polymorphonuclear leukocytes. Organization proceeds throughout the exudate in the lumen and the plicae become adherent

The fimbriated extremity is obliterated and the end is sealed as a bulbous, smooth structure. If both ends of the tube are obliterated by fibrous tissue the lumen is distended with pus—pyosalpinx. With resolution the pus is converted into a thin, limpid, colorless fluid—hydrosalpinx. Gonococci can be cultured from the pus and tissues in about two-thirds of the examples of subacute and chronic salpingitis (Studdiford, Casper, and Scadron). Surgeons have noted a high frequency of delicate, strandlike adhesions between the liver and the anterior abdominal wall in women with salpingitis. During the acute phase of salpingitis there is not infrequently pain in the right upper quadrant of the abdomen (Hertz).

TUBO-OVARIAN ABSCESS. In some instances the free extremity of the tube becomes adherent to the adjacent ovary. Abscesses form

within the ovary, and a large cavity representing the former lumen of the tube and the center of the ovary is formed—tubo-ovarian abscess. The wall of this abscess is made up of a loose, fibroblastic tissue, infiltrated with numerous mononuclear cells and plasma cells. Many of the mononuclear cells are distended with small vacuoles.

Gonococcal Vulvovaginitis. Before the days of modern hospital practice, vulvovaginitis in children was largely a hospital and institutional disease, spread by contaminated towels

ceration and vascularization. In healing, scar tissue is formed, and blindness results. In the last century, approximately 28 per cent of all blindness in children was caused by gonococcal ophthalmia, but at the present time the percentage is less than 7, a decrease directly attributable to the prophylactic use of silver nitrate in the eyes of newborn infants.

Miscellaneous Lesions. In sexual perverts gonorrhea of the rectum has been reported. The mucous membrane is swollen, velvety, red, and covered with a purulent exudate. The



Fig. 181. Chancroid. (Fordyce.)

and linen. With the elimination of this source, infection today is largely direct (because of sexual curiosity) or indirect (through towels) from gonorrheal adults of the family. Transmission by way of toilet seats has not been demonstrated (Rice, Cohn, Steer, and Adler). Pathologic changes are similar to those in adults in the vulva, but there is in addition a purulent inflammation of the vagina. Most investigators report that treatment with estrogens is highly satisfactory. The spread to the tubes in children is unusual, but gonorrheal peritonitis has been reported (Bloch, Pacella, and Locastro).

Gonococcal Ophthalmia. Gonococci present in the birth canal may be inoculated onto the conjunctiva during passage of the fetus. Within two or three days there is acute suppurative inflammation of the cornea with ul-

lesion stops sharply at the anorectal junction. In certain persons with genital gonorrhea, lesions of the skin, more commonly on the trunk, may be associated with the appearance of a gonococcal septicemia. There are vesicles and papules, symmetrically arranged. Healing occurs by desquamation.

Causal Agent. The gonococcus is a characteristic gram-negative diplococcus, found in the body fluids intracellularly. Special culture media and conditions are desirable for isolation of the organism (Reid). No disease similar to that in man has ever been reproduced in experimental animals (Trussell and McNutt), but injections of the organisms into mice and other animals in large amounts produce fatal toxemia (Miller and Hawk). There is no lasting immunity to the gonococcus and an acute attack of urethritis can start during

the chronic phase of a previous attack. This phenomenon is probably related to the fact that the cocci in the urethra do not penetrate deeply into the tissues. In many of the chronic lesions it is not possible to demonstrate the bacterium by either staining or cultural methods (Cohn, Grunstein, and Heaton). For example gonococci can be recovered from the pus in only 25 per cent of cases of gonococcal arthritis.

Chancroid

The venereal disease known as chancroid or soft chancre is caused by the bacterium *Hemophilus ducreyi* (Greenwald).

Pathologic Anatomy. The initial lesion is a small papule or vesicle that rapidly proceeds to the formation of a pustule. The pustule ruptures and there results a sharply circumscribed ulceration with ragged, undermined edges. The base of the ulcer is filled with a gray exudate and when this is removed there are a few punctiform foci of bleeding. Microscopically, an edema of the epidermis and invasion of the swollen epithelial cells by polymorphonuclear leukocytes are observed in the early lesion. The intra-epidermal abscesses spread in both directions rupturing onto the surface and eroding into the dermis. In the surrounding connective tissue there is a dense infiltration, especially perivascularly, with polymorphonuclear leukocytes and a few plasma cells. At the edges of the ulcer there is a marked acanthosis. Blood vessels and lymphatics over a large area are dilated (Sheldon and Heyman). The most common locations in men are at the preputial orifice, the internal surface of the prepuce, the frenum, and the fossa navicularis. In women chancroid occurs most frequently on the labia minora, clitoris, fourchette, and vestibule (Allison). The regional lymph nodes in over one-half the cases are enlarged and the centers undergo suppuration. In a small percentage the lymph nodes become adherent to one another and ulcerate through the skin surface. Histologically an acute purulent inflammation similar to that in the initial lesion is observed. There is no evidence that *Hemophilus ducreyi* invades the body beyond the first regional lymph nodes. Occasional examples of extra-genital chancroid are observed.

Causal Agent. *Hemophilus ducreyi* is diffi-

cult to identify in smears. Special culture media containing blood must be used for isolation. A similar disease can be produced in monkeys and rabbits, and auto-inoculation in man is not infrequently observed.

Predisposing Factors. Chancroid is seen in persons who live in filth and squalor. It is more common in Negroes and in the Orient than in any other race or geographical region. The organism invades the skin through a small traumatic wound and phimosis is a predisposing factor.

Clinicopathologic Correlation. Lesions appear in from one to four days after contact. The edema and hyperemia in and about the ulcer lead to pain. In women, *Hemophilus ducreyi* is frequently found as a saprophyte in the vagina, and hence most new cases appear after coitus with prostitutes. The ulcer heals in from six days to many months. A few are progressive and produce large spreading lesions. Occasionally an ulcer on the genital organs represents a mixture of syphilis and chancroid and is known as a mixed chancre (Sullivan).

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XLIV

Miscellaneous Venereal Diseases

Aside from syphilis, gonorrhea, and chancroid, venereal disease includes venereal lymphopathy, acuminate condyloma and venereal fusospirochetosis.

Venereal Lymphopathy (Venereal Lymphogranuloma)

Pathologic Anatomy. *Genital Lesions.* The initial lesion, which appears from a week to

After several weeks there is enlargement of the inguinal lymph nodes on one or both sides. These nodes are firm, with dense fibrous adhesions to the surrounding tissue. Several nodes frequently form a large, confluent mass adherent to the overlying skin. On section of the node numerous small cavities are seen, 1 to 2 mm. in diameter, filled with a thick, yellow, viscid fluid. The intervening tissue is gray and firm. The earliest microscopic lesion

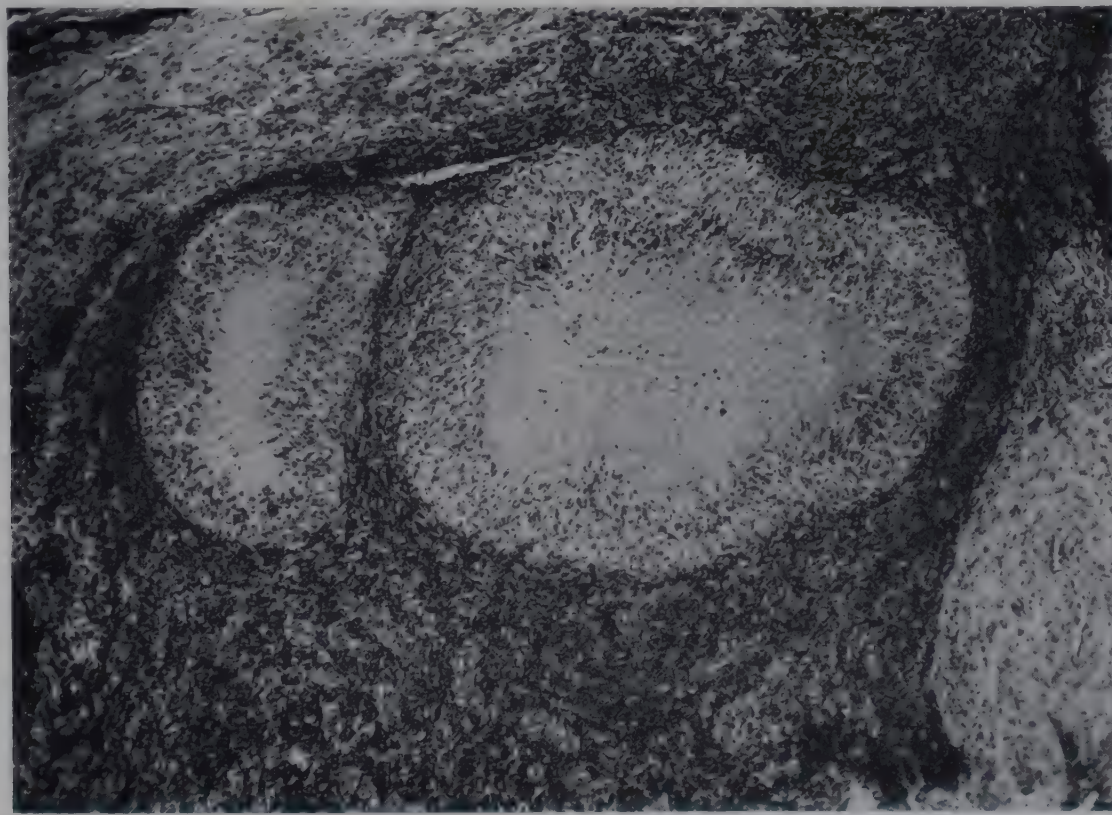


Fig. 182. Venereal lymphopathy with granulomatous lesions in lymph nodes. (Tissue by courtesy of Captain Edward Smith, A.U.S.)

several months after exposure, is a small, indurated, nontender, herpetiform nodule on the prepuce or on the vulva which frequently ulcerates. The base of the ulcer is formed by a zone of necrosis resting on granulation tissue infiltrated with leukocytes. About the ulcer there is infiltration of the dermis with plasma cells and lymphocytes and rarely small granulomas.

is a focal infiltration with leukocytes, followed rapidly by increase of lymphocytes and plasma cells and suppuration. The small necrotic foci coalesce to form the classical "stellate abscesses." Later a marginal zone of epithelioid cells and fibroblasts forms. Healing occurs by fibrosis. The capsule of the node participates in the inflammation. The blood vessels show a proliferative endarteritis. The formation of

sinus tracts through the skin is not uncommon (Smith and Custer).

Lesions of the Colon. The primary lesion of the colon in venereal lymphopathy is in the rectum, and consists of the formation of deep ulcers, discrete or confluent (Grace). The ulcers penetrate to the serosa and may connect with one another to form fistulous tracts, undermining the wall of the rectum. Occasionally these fistulous tracts dissect through the perirectal tissue and open on the skin of the perineum. Rarely the lesions extend throughout the entire large intestine (Barber and Murphy). With further progress, there is fibrosis of the wall, either diffuse or local, with the formation of strictures. The veins frequently contain thrombi, with or without associated phlebitis. The draining lymph nodes are enlarged and on section show small foci of necrosis. Microscopically there is the typical picture of the disease—multiple foci of suppuration in the early stages and fibrosis in the later stages. Rarely there is thrombophlebitis of the superior hemorrhoidal veins with multiple abscesses of the liver due to secondary bacterial infection. In a significant number of instances venereal lymphopathy of the colon is associated with carcinoma.

Systemic Lesions. There are reports of conjunctivitis and meningitis (Scott) from which the virus has been isolated. In addition examples of ulcerative colitis, enteritis, pharyngitis, salpingitis, dermatitis, and arthritis have been attributed to venereal lymphopathy. In most instances the diagnosis rests on histologic change or the Frei test (Koteen).

Causal Agent. The cause of venereal lymphopathy is a virus. Intracerebral inoculation of mice results in a meningo-encephalitis. The virus may be cultured in the chick egg or in tissue cultures. A preparation of pus from a lymph node injected into the skin of a patient with the disease gives a reaction—the Frei test.

Condyloma Acuminatum

One of the rare forms of venereal disease is the condyloma acuminatum or venereal wart. These warts occur on the skin or mucous membrane of the genitorectal region as papillary elevations, supported on a narrow stalk.

Histologically tremendous acanthosis and elongation and broadening of the rete are observed. The blood vessels in the connective tissue stalk are dilated and there is a moderate infiltration with lymphocytes, plasma cells, and leukocytes. There are occasionally many mast cells. Within the nuclei of the epithelial cells there are occasional basophilic inclusion bodies.

Experimental investigations indicate that the venereal wart is caused by the same virus that produces warts on other parts of the body.

Venereal Fusospirochetosis

Among the Negroes of the South one of the important venereal diseases is that resulting from the spirochete and the fusiform bacillus. Lesions are most commonly found on the prepuce and glans in men and in the deeper recesses of the vulva and the vagina in women. Small or large spreading ulcers with an indurated, firm, elevated edge are produced. At the edges of the ulcer there are acanthosis and elongation of the rete pegs. In the bed of the ulcer there are a necrosis of tissue and a heavy infiltration with polymorphonuclear leukocytes. When severe, there may be gangrene of the shaft of the penis—gangrenous balanitis (von Haam).

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XLV

Diseases Caused by Bartonella

The genus *Bartonella* includes a group of micro-organisms found in various animals in close association with the red blood cell. They are parasitic, either on the surface or within the red cell, and under certain conditions bring about destruction of it and an anemia. In man only one disease, Carrión's disease, is

the Andes Mountains between 6° and 13° south latitude. Carrión was a Peruvian physician who inoculated himself and subsequently died of the disease. From both a clinical and pathologic standpoint it is divisible into two distinct types: Oroya fever and veruga peruviana. The former is characterized

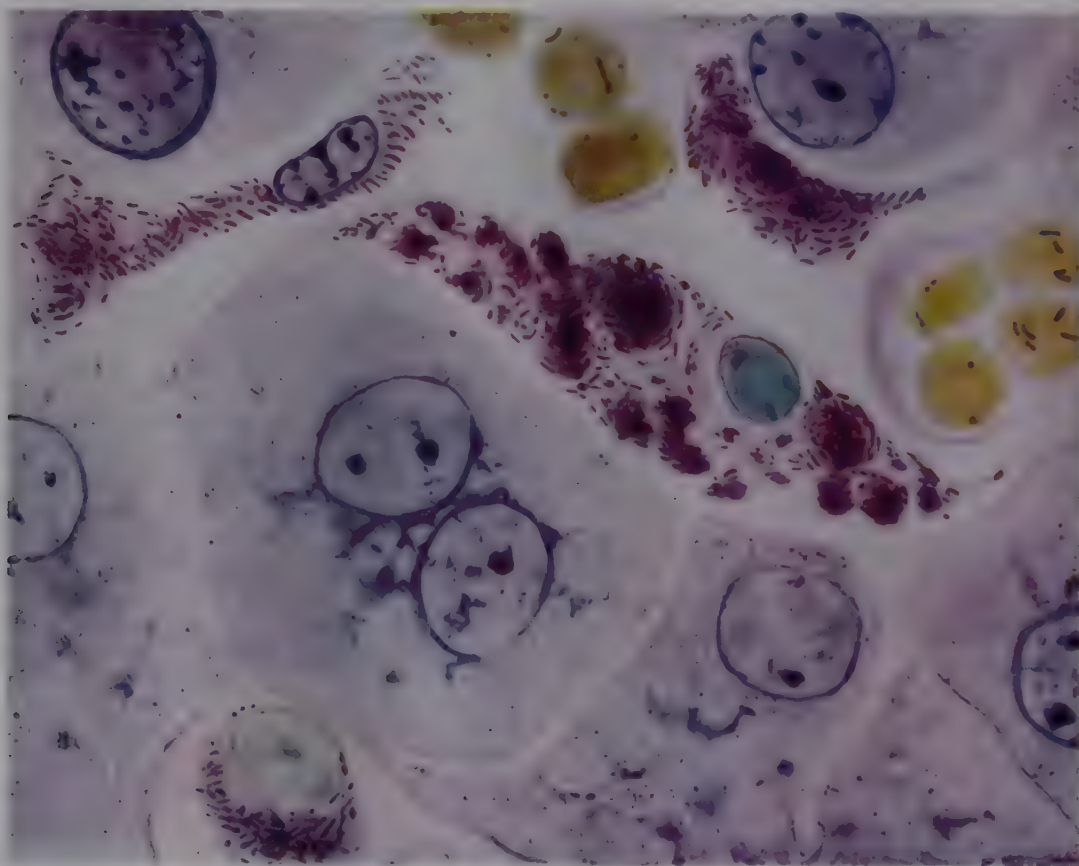


Fig. 183. Liver in Carrión's disease. (From a drawing by Miss Piotti for Dr. Henry Pinkerton.)

known to be caused by *Bartonella*. In animals there are a number of latent infections caused by organisms of this genus. They are of interest because of the relation of the spleen to the disease, and they form the basis of a great deal of our knowledge of the role of the spleen in defense against latent infection.

Carrión's Disease

Carrión's disease is a condition found in certain narrow valleys on the western slopes of

by an acute course, with extreme anemia; while the latter is a chronic condition with a less severe anemia and a nodular eruption on the skin, which lasts for weeks or months.

Oroya Fever. In fatal cases the skin, mucous membranes, and viscera are pale. The lymph nodes are enlarged and soft. The endothelial cells are edematous and hyperplastic, and are filled with *Bartonella*. The liver is enlarged and shows focal and central necrosis. The Kupffer cells are filled with hemosiderin. The spleen is enlarged and contains numerous

small infarcts. Hyperplasia of endothelial cells and parasitism by Bartonella may be seen microscopically. The bone marrow of all bones is soft and red, and shows intense hyperplasia of the erythroid series of cells and slight to moderate hyperplasia of the myeloid series of cells. The heart is dilated and shows fatty degeneration of the myocardium. The clinical course extends only over a few weeks, and the signs and symptoms are dependent upon the presence of an infection and the profound anemia. The mortality averages from 40 to 50 per cent.

Verruga Peruviana. Over the skin, more especially on the extensor surfaces of the arms and legs and on the face, there are small, bright red, sessile or pedunculated nodules, 1 to 10 mm. in diameter. On the mucous membranes of the respiratory, alimentary, urinary, and female genital tracts there are similar but usually smaller nodules. Microscopically, proliferation of the capillary endothelium may be seen, and in the capillaries and the interstitial spaces of the tissue there are large mononuclear cells. Both types of cells are filled with Bartonella. Microscopic hemorrhage and necrosis is the rule, but gross hemorrhage, necrosis, and ulceration are rare. Occasionally secondary bacterial infection supervenes, and death may result from a septicemia. After some weeks or months the nodules gradually disappear, leaving no scar unless there has been superficial ulceration. The mortality is low unless there is secondary bacterial infection.

Causal Agent. Both conditions are caused by a small, rod-shaped micro-organism, Bartonella bacilliformis, readily identified in tissue sections and in blood. The organism is gram-negative, and stains a reddish violet with Giemsa's stain. It may be cultured on leptospiral medium and in tissue culture (Pinkerton and Weinman). Verrucous nodules and anemia have been produced in monkeys by the inoculation of tissue or of pure cultures.

Transmission. Bartonella bacilliformis is apparently found only in man. Some hematophagous arthropod is presumably the vector, probably Phlebotomus noguchi (Weinman and Pinkerton).

Bartonellal Infection in Animals. At least three other species of Bartonella are known: Bartonella muris of the rat, Bartonella canis of the dog, and Bartonella tyzzeri of the guinea pig (Kikuth). A somewhat similar parasite, Eperythrozoon coccoides, is found in the red blood cell of mice after splenectomy.

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XLVI

Diseases Caused by Rickettsiae

Rickettsiae may be defined as gram-negative, intracellular organisms with a bacteriumlike morphology. They were first recognized by H. T. Ricketts, of the University of Chicago, during an investigation of Rocky Mountain spotted fever.

Types of Rickettsial Disease. The known rickettsial diseases of man may be arranged in five main groups: typhus, spotted fever, tsutsugamushi disease, Q fever, and trench fever. Within the typhus group there are the epidemic or human type and the endemic or murine type. Spotted fever includes Rocky

mals, depending upon the virulence of the organism. In the rabbit there is little evidence of disease, but antibodies against *Proteus vulgaris* are developed. Several varieties of monkey are susceptible, and in some instances the typical clinical disease and pathologic changes occur. Rats and mice are in general not susceptible, but exposure to irradiation will render mice highly susceptible.

Transmission. Insects are the direct vectors of all rickettsial diseases. Ticks are the vectors of spotted fever, *fièvre boutonneuse*, Q fever, tick typhus of Siberia, India, Australia, and

TABLE 22. THE WEIL-FELIX REACTION

	Agglutination with		
	OX-19	OX-2	OX-K
Epidemic typhus	++++	+	0
Endemic typhus	++++	+	0
Tsutsugamushi	0	0	++++
Q fever	0	0	0
Spotted fever	++	++	0

Mountain spotted fever, *fièvre boutonneuse*, and rickettsialpox. Trench fever has not been proved to be a rickettsial disease (Pinkerton).

Cultivation. The rickettsiae are obligate, intracellular parasites and have been grown in tissue culture, on agar slants with added living tissue, and on the chorio-allantoic membrane, in the yolk sac, and in the embryo of developing chick eggs (Cox).

Pathogenicity for Animals. In general, all of the rickettsiae produce pathologic change in the tunica vaginalis of the male guinea pig after intraperitoneal injection. Experimental typhus fever is rarely lethal, while spotted fever kills a variable percentage of the ani-

Africa, and Kenya typhus. Mites are the vectors of tsutsugamushi disease and rickettsialpox, and possibly of some murine typhus. The louse and flea are the vectors of epidemic typhus and trench fever and of endemic typhus respectively (Kohls).

Immune Reactions. During an attack of a rickettsial disease, antibodies of various types appear in the serum. These may be classified from a diagnostic standpoint in decreasing order of importance as complement binding, agglutinating for *Proteus vulgaris*, and agglutinating for rickettsiae. In addition neutralizing antibodies may be demonstrated by passive transfer. Agglutination of the various

strains of *Proteus vulgaris* is known as the Weil-Felix reaction and is valuable in diagnosis as shown in Table 22. The explanation of the Weil-Felix reaction is probably that the *Rickettsia* and *Proteus* contain a common antigenic substance (Castaneda).

Saprophytic *Rickettsia*. A wide variety of arthropods contain within their cells small coccobacillary structures identical with the *Rickettsia* known to produce disease. The significance of these is not known at the present time, and a sharp line of distinction between the larger rickettsiae and the smaller bacteria cannot be drawn (Hertig and Wolbach; Cowdry).

Epidemic Typhus Fever

Whenever war, famine, or misery has visited a part of the human race, various epidemic diseases have followed, the most important of which is typhus fever. The first outbreak in western Europe that can be certainly identified came at the siege of Granada in 1489, when 17,000 soldiers of King Ferdinand died of a fever designated by them as "tabardillo." Since that time there have been well over one hundred major epidemics, and the toll of human life is best suggested by one figure—180,000 cases in Poland in the year 1919. In England there were many epidemics, and the prisons were so badly infected that it was dangerous to hold court in the presence of the prisoners. In North America the principal epidemics were in Quebec and Montreal in 1820, in Halifax in 1827, in Boston in 1838 and 1847, in New York in 1818–1825, 1837, 1847, 1852, 1881, and 1892, and in Philadelphia in 1827, 1836, and 1847 (Vaughan; Dyer). The last great epidemics were in Serbia in 1915 (Strong, Shattuck, Sellards, Zinsser, and Hopkins), and in Poland during World War I and after it (Wolbach, Todd, and Palfrey). Active preventive measures limited spread of the disease during World War II. Current endemic regions are shown on the map on page 357.

Up until 1836 clinicians did not accurately distinguish between typhus and many other infectious fevers, particularly typhoid. In that year Gerhard, an American physician in Philadelphia, had just returned from Paris, where, under the great French clinician Louis, he had learned to recognize typhoid at the autopsy

table by the lesions of the lymphoid follicles of the intestine. When he studied at autopsy the fatalities during the epidemic in Philadelphia in 1836 he noted the following: "The anatomical characters of these varieties of fever are peculiar to themselves, and it is as impossible to substitute the lesions of the follicles of the small intestine observed in the typhoid fever for the pathological phenomena of typhus, as it is by treatment or other means to transform the eruption of measles into the pustules of small pox."

Pathologic Anatomy. The *gross findings* in a patient dead of typhus fever are not conspicuous. The larger ecchymoses in the skin persist, but many of the small petechiae are not as visible as during life. There may be small or large areas of necrosis of the skin of the trunk or extremities. The heart is slightly dilated, and the myocardium is pale and yellow. The larger blood vessels in general show no change, but there may be thrombosis of arteries such as the superior mesenteric, splenic, or iliac. The spleen is moderately enlarged, firm, and dark red. The lymph nodes are not remarkable. The bone marrow is red and cellular. The mucosa of the bronchi is swollen and red, and in the lungs in most fatal cases there is a typical bronchopneumonia. There are occasional petechiae in the mucosa of the alimentary tract. The liver is slightly swollen, and occasionally there are small foci of necrosis. The kidney is swollen and pale. There are rare petechiae in the pelvis, ureters, and bladder. The brain is slightly edematous and congested (Ceelen).

The typical *microscopic lesion* of typhus fever is a nodular type of inflammation associated with small blood vessels. The endothelium of the capillaries is swollen and the cells filled with rickettsiae. About the involved vessel there is an accumulation of mononuclear cells, lymphocytes, plasma cells, and a few polymorphonuclear leukocytes. In slightly larger vessels small mural thrombi form on the surface of the swollen endothelium. In contrast with Rocky Mountain spotted fever, there is rarely necrosis of the wall of the vessel. In some areas, especially the skin, this focal inflammation is associated with hemorrhage. This type of lesion is found in all the organs of the body to a greater or less extent. In the myocardium there is a diffuse as well as a focal inflammation, characterized by

edema and infiltration with mononuclear cells and lymphocytes. Isolated myocardial fibers or groups of fibers show necrosis.

In the liver the Kupffer cells are swollen, and there are small foci of necrosis. There are focal lesions in the skeletal muscle, with occasional Zenker's degeneration of the fibers. The spleen and the lymph nodes show a non-specific type of hyperplasia. There is myeloid and erythroid hyperplasia of the bone marrow (Wolbach, Todd, and Palfrey; Ceelen).

The most characteristic histologic lesion of typhus is in the brain. Throughout all parts of

lowed by recovery. Blood taken during the febrile period will infect other guinea pigs, and the organism can be propagated by serial passage. The rickettsiae are found in the cells of the tunica vaginalis, and pathologic lesions identical with those in man, but less severe, are present in all of the organs.

Transmission. Typhus fever is transmitted from man to man by the body louse, *Pediculus humanus corporis*. The rickettsiae can be demonstrated in the body of a louse fed on an ill person, and there are a few instances of the experimental transmission of typhus to man.

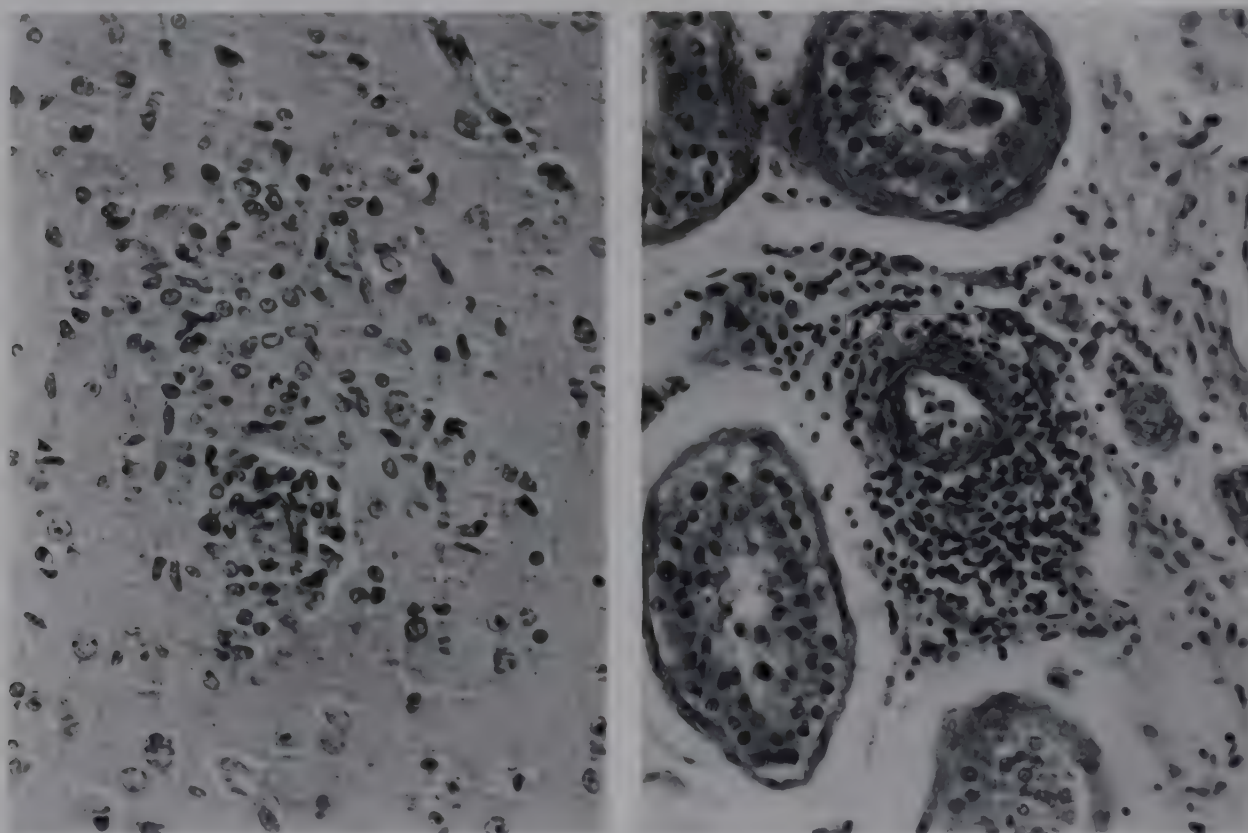


Fig. 184. Brain and testis in typhus fever. (Photographs by courtesy of Prof. C. H. Hu.)

the brain, more in the gray matter than in the white matter, except at the base, there are the typical typhus nodules, usually formed about a small capillary. The nodules are composed of swollen endothelium and peripheral collections of rod cells (probably microglia), large mononuclear cells, lymphocytes, and an occasional polymorphonuclear leukocyte (Fig. 184). Rarely there is hemorrhage into these nodules. In the remainder of the brain there is a perivascular infiltration with lymphocytes. The meninges show slight or no reaction.

Causal Agent. The infecting agent of epidemic typhus may be isolated from the blood or from the tissues by injection into monkeys or male guinea pigs. In the monkey the disease produced and the pathologic lesions are similar to those of human typhus. In the guinea pig a transient fever of four to six days is fol-

The control of endemic and epidemic foci is entirely a matter of the control of lice. In Serbia in 1915 delousing of an entire nation brought one of the worst epidemics in history within bounds in six months (Strong, Shattuck, Sellards, Zinsser, and Hopkins). Undoubtedly there are other factors which determine the outbreak of an epidemic beyond the presence of infected body lice. It has been demonstrated, for example, that riboflavin deficiency in rats lowers the resistance of this animal to the *Rickettsia* of endemic typhus (Pinkerton and Bessey).

Clinicopathologic Correlation. The incubation period is five to twenty-one days, and the stage of invasion is marked by the sudden onset of fever, headache, prostration, and anorexia. The usual febrile course terminates in about thirteen days. The pathologic lesions in

the small blood vessels of the skin are responsible for the maculopapular eruption that appears on the fourth or fifth day (Fig. 189, p. 361). The face and head are rarely if ever affected. The interstitial myocarditis and de-

The pathologic changes in the central nervous system in general give only nonspecific signs and symptoms: stiffness of the neck, positive Kernig sign, sluggish reflexes, and hyperesthesia. During the early stages the in-

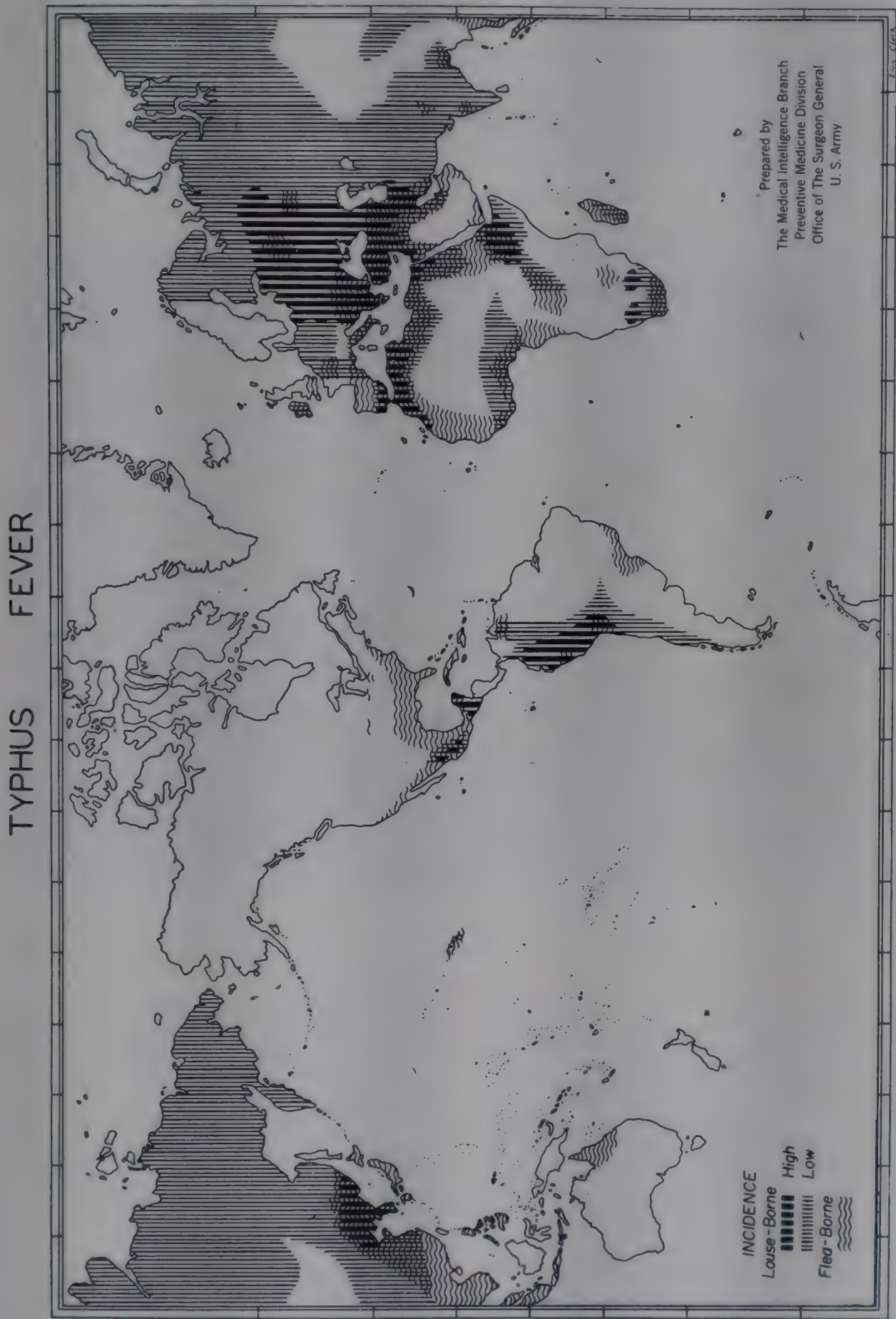


Fig. 185. Worldwide distribution of typhus fever.

generation of the myocardial fibers are related to the low blood pressure, poor quality of the pulse, indistinct heart sounds, and occasional murmurs. The spleen and liver are usually not sufficiently enlarged to be palpable below the costal border.

flammation of the brain is associated with an excited delirium, but later there is mental dullness or coma. The degenerative changes in the kidney produce oliguria and albuminuria. Secondary bacterial infections of the lungs and of the parotid gland are not uncommon, espe-

cially in fatal cases. The symmetrical gangrene of the extremities cannot be clearly explained. It is probably related both to vascular supply and to lesions in the central or peripheral nervous system. Indefinite signs and symptoms related to the internal viscera are probably dependent on lesions in the vagus nerve and in the sympathetic nervous system (Herzog and Rodriguez). The deafness frequently seen as a sequela is due to a complicating suppurative otitis media, and is not the direct result of the rickettsiae.

turies (Ricketts and Wilder). In the 1920's an identical disease was found to be prevalent in the southeastern United States, particularly in Alabama and Georgia. Other features which distinguished this disease from European typhus were the lower mortality rate, rarely exceeding 5 per cent, and the higher incidence in summer and fall (epidemic typhus occurs in the winter and spring).

Pathologic Anatomy. The pathologic changes in the tissues in endemic typhus are similar, if not identical, to those of epidemic

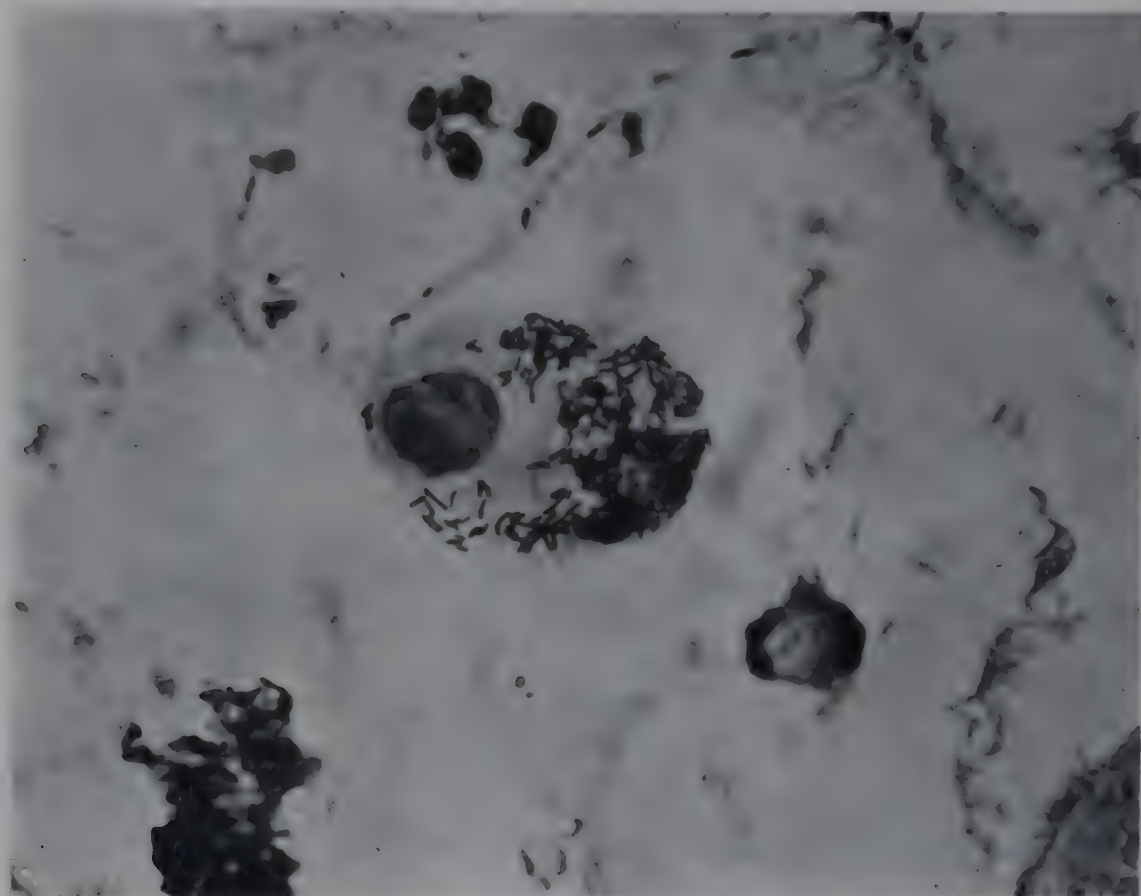


Fig. 186. Rickettsiae in endemic typhus. (Armed Forces Institute of Pathology, Neg. No. 73585.)

Endemic Typhus Fever

Shortly after the conquest of Mexico by the Spaniards, European or epidemic typhus was introduced into that country. Through the migrations of the people of eastern Europe and of Ireland to the United States, epidemic typhus was also introduced into this country. Around 1900 certain peculiarities of typhus fever on the North American continent were noted. Brill in 1898 and subsequently in 1910 gave an accurate clinical description of a disease in New York City which could be nothing but typhus, yet there was evidence that it could not have been transmitted from man to man by the louse. The same conditions were found to be true in Mexico, where Mexican typhus or tabardillo had been known for cen-

typhus. They differ only in severity and extensiveness.

In guinea pigs there is conspicuous scrotal swelling, usually not seen in classical typhus (Mooser and Dummer).

Transmission. It was shown before 1930 that Brill's disease, tabardillo of Mexico, and endemic typhus of the southeastern United States are all transmitted by the rat flea, *Xenopsylla cheopis* (Dyer, Ceder, Rumreich, and Badger; Mooser and Castaneda); and by the rat louse, *Polyplax spinulosus*. The reservoir of the disease is in rats. The virus may persist in them for as long as a year. Just as epidemic typhus can be brought under control by the eradication of the human body louse, endemic typhus can be controlled by the extermination of rats. In 1934 a campaign was

inaugurated in Alabama, and there were only 60 cases of typhus in 1934 as compared with 288 for the same period of the preceding year. However, the disease has apparently spread northward and sporadic cases are observed north of the Ohio River.

Clinicopathologic Correlation. The clinical signs and symptoms are similar to those of epidemic typhus. The Negro of the South is relatively free of the disease, and it occurs more frequently in men in the ratio of 2 to 1. Complement fixation may be of value in diag-

passed from man to man by the human louse, may again take on its original characteristics (Zinsser, Castaneda, and Mooser). However, this has not been proved.

Spotted Fever

According to an old Indian legend, the Bitter Root Valley in Montana was visited each spring by evil spirits. With the settlement of Montana by the white man in the late nineteenth century, these evil spirits were recog-

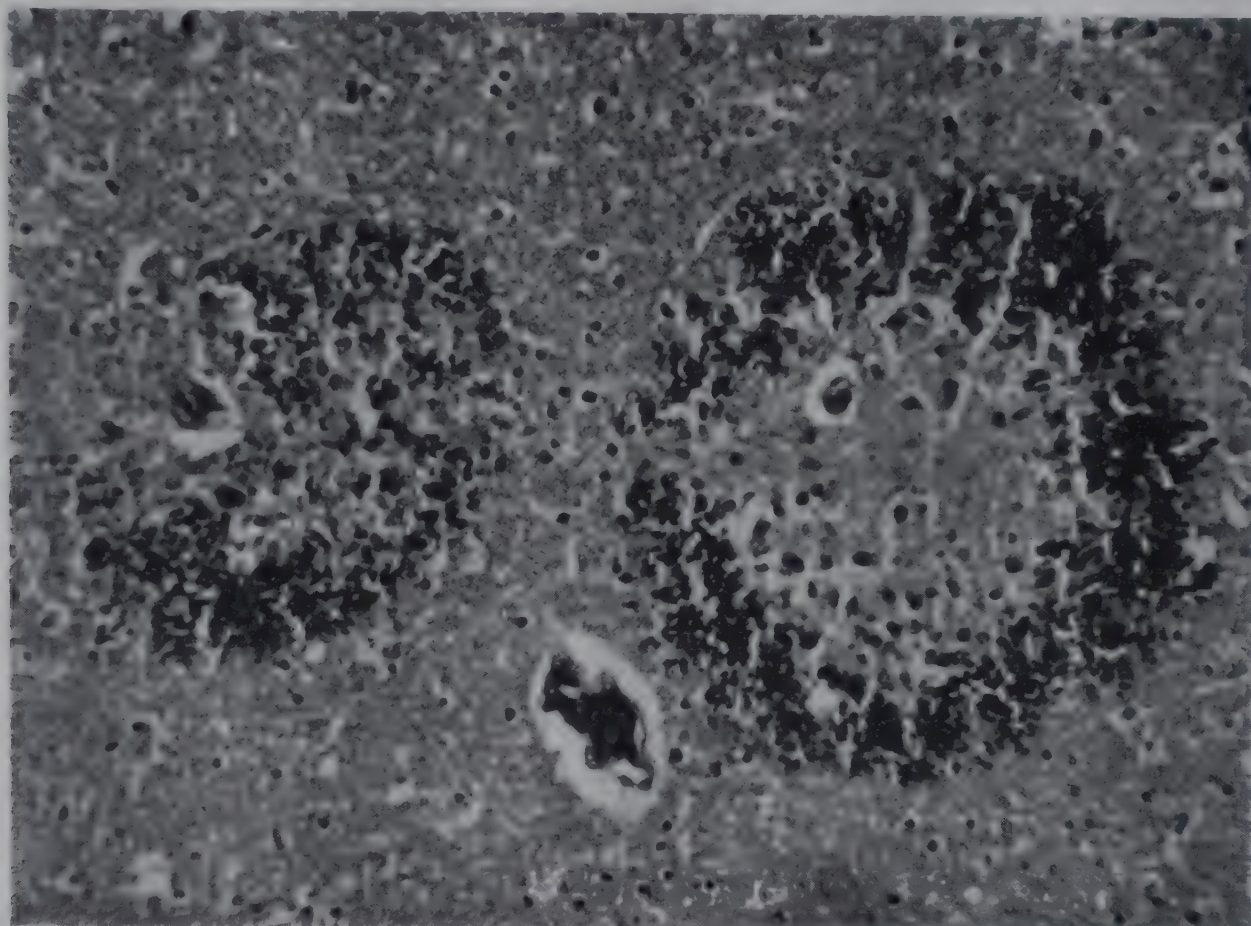


Fig. 187. Ring hemorrhage in brain in spotted fever. (Armed Forces Institute of Pathology, Neg. No. 63759.)

nosis (Castaneda). The agglutination with *Proteus* is of the typhus type.

Other Varieties of Endemic Typhus. Probably identical diseases in other parts of the world are South African typhus, shop or urban typhus of Malaya, and ship typhus of Toulon.

Relation of Epidemic to Endemic Typhus. The causal agents of these two varieties of typhus are similar, and there has been considerable speculation as to their relation. The *Rickettsia* of endemic typhus differs antigenically and in virulence from that of epidemic typhus. It seems most probable that the *Rickettsia* of epidemic typhus, when introduced into the rat flea and into the rat, becomes slightly modified; and that on occasion this modified virus, reintroduced into man and

nized as a disease which came to be known as "Rocky Mountain spotted fever." Scientific investigation in the early twentieth century confirmed the observations of the Indians that the condition was more prevalent in certain valleys than in others. About 1930 the same disease was recognized along the Atlantic seaboard, and cases have now been observed in most of the states and in several foreign countries (Hampton and Eubank).

Pathologic Anatomy. The pathologic changes are in large part dependent on the duration of the disease. If the patient dies before the tenth day, they are inconspicuous. The mottling of the skin, and to some extent the petechiae, disappear after death and are not clearly defined at the autopsy table. There

is generally a slight icterus, and occasionally a generalized edema of moderate proportions. The skeletal muscles are either pale or dark red, and rarely there is the hemorrhage into the recti muscles characteristic of many severe infections. There are petechiae in the serous membranes. The lungs show congestion and edema, and in many cases after the tenth to the twelfth day there are definite grayish red nodules of bronchopneumonia. The lymph nodes throughout the body are slightly enlarged, congested, and edematous. The heart is of normal size, and the myocardium is pale. There may be petechiae or ecchymoses in the mucosa of the gastro-intestinal

and gram-positive cocci can be stained in the tissues, indicating that this is a secondary infection. In the myocardium there is an interstitial, inflammatory reaction characterized by edema, congestion, and infiltration with lymphocytes and smaller numbers of plasma cells, monocytes, and neutrophilic or eosinophilic leukocytes. In the liver there are an excessive infiltration of lymphocytes into the portal canals, fatty degeneration of the liver cells, swelling of the Kupffer cells with phagocytosis of nuclei and red blood cells, and occasional areas of focal necrosis. In the spleen the follicles are small, and the splenocytes in the red pulp are swollen. In the lymph nodes there



Fig. 188. *A*, *Dermacentor andersoni*, major vector of spotted fever in the West. *B*, *Dermacentor variabilis*, common eastern dog tick, which is a vector of spotted fever in the East. (Sharp and Dohme Seminar, Vol. 4, No. 2.)

tract. The liver is of normal size and shows cloudy swelling. The spleen is enlarged, averaging 280 gm. The pulp is deep purplish red and soft. The kidneys are pale and slightly swollen.

The characteristic *microscopic lesions* are necrosis of the walls of small arterioles and venules, thrombosis within the lumen, and cellular infiltration, especially perivascularly, with lymphocytes (Fig. 187). The lesions are found in the skin and in all the viscera. Within the endothelial cells and in the smooth muscle cells of these lesions *Rickettsia* can be identified. The rickettsiae occur as intracellular clusters of minute coccoid, sometimes diplococcoid, and solid or bipolar, bacillary forms.

The bronchopneumonia is of the usual type,

are congestion, edema, and desquamation of the endothelial cells of the sinusoids. The bone marrow shows a slight hyperplasia of the myeloid elements.

In the brain there are three types of focal lesions: perivascular infiltration of lymphocytes with swelling of the endothelium and thrombosis; proliferation of glial tissue to form nodules either around or at a distance from blood vessels; and necrosis and thrombosis of small arterioles with resultant miliary infarcts of the brain. There is often a slight lymphocytic infiltration into the choroid plexus and the meninges. Focal lesions are found in all parts of the brain but are more common in the white matter (Lillie; Wolbach).

Causal Agent. The rickettsia of spotted

fever is most readily isolated by the intraperitoneal injection into male guinea pigs of from 2 to 4 cc. of whole blood. On the second to the fifth day a fever develops, and in most instances congestion, edema, and even necrosis of the scrotum follow within another two to four days. As the disease is not invariably fatal, the animal should be sacrificed during the height of the reaction, and the cells and exudate of the tunica vaginalis studied for the presence of rickettsiae. In explants of infected spleens in tissue culture the rickettsiae grow within the nuclei, a pathognomonic characteristic of the spotted fever rickettsiae. The pathologic changes in the guinea pig are identical with those in man. The organism grows readily in the yolk sac of the developing chick embryo (Cox). Complement-binding bodies are present in the serum of recovered patients.

Transmission. In the region of the Rocky Mountains, spotted fever is disseminated by the wood tick, *Dermacentor andersoni*. In the central and eastern United States the dog tick, *Dermacentor variabilis*, is the responsible insect. Throughout all of the United States, Canada, and Central America, the rabbit tick, *Haemaphysalis leporis-palustris*, carries a relatively avirulent strain of the *Dermacentroxenus rickettsi*. From 1 to 5 per cent of all wood ticks in the Rocky Mountains are infected with rickettsia. The larvae and nymphs engorge on a variety of small rodents and carnivores, while the adult forms bite man and larger animals.

The seasonal incidence of spotted fever varies with the part of the country, and the type of tick involved. In the Rocky Mountains the highest morbidity is during June, while in the eastern United States the crest is not reached until July and August. The infection is transmitted hereditarily in the tick.

The rabbit tick is also found on birds, and possibly these animals serve as a further reservoir for the disease (Parker).

Clinicopathologic Correlation. The incubation period varies from three to twelve days, and the tick must attach itself to the body for one-half hour to several hours to produce a human infection. In general the severity of the disease is directly dependent on the time-period of attachment of the tick. The invasion of the body is marked by malaise, chill, pain in the muscles and bones, headache, fever, and rapid pulse and respira-

tion. The edema and congestion of the lungs and bronchi result in a slight, nonproductive cough. By the third to the fifth day the necrosis and thrombosis of the small blood vessels result in hemorrhage visible on the surface of the body as petechiae or ecchymoses. These are at first small macules which disappear on pressure, but later are deep red or purple,



Fig. 189. Typical hemorrhagic rash of spotted fever on lower extremities. (Armed Forces Institute of Pathology, Neg. No. 49096.)

confluent, and cannot be pressed out. The occlusion of blood vessels manifests itself in the necrosis of skin of the scrotum, fingers, toes, and ears.

Pathologic changes in the liver usually result in icterus during the second week. The lesions of the brain produce no localizing symptoms or signs but are probably related to the restlessness, insomnia, hyperesthesia, and drowsiness. The hyperplasia of the bone marrow is reflected in a slight elevation of the circulating white cells with a relative lymphocytosis. The degenerative changes in the

kidneys are related to an oliguria and albuminuria. The spinal fluid either is normal or shows a slight pleocytosis because of the minimal meningeal inflammation. No local lesion develops at the site of the bite, and it frequently cannot be identified. There are undoubtedly many abortive and subclinical cases.

Recovery is usually complete, although permanent damage to certain structures may result in deafness, impaired vision, insomnia, or anemia (Parker). The use of the newer antibiotics has reduced the mortality rate to only a few per cent.

condition, nothing is known concerning pathologic changes.

Q Fever

In 1935 a new clinical entity, designated "Australian Q disease," was described in workers in abattoirs of Queensland, Australia (Derrick). A rickettsia was isolated and subsequently named *Rickettsia burneti* (Burnet and Freeman). In 1938, as a part of the investigation of the ticks in Montana, a hitherto unknown rickettsia was identified

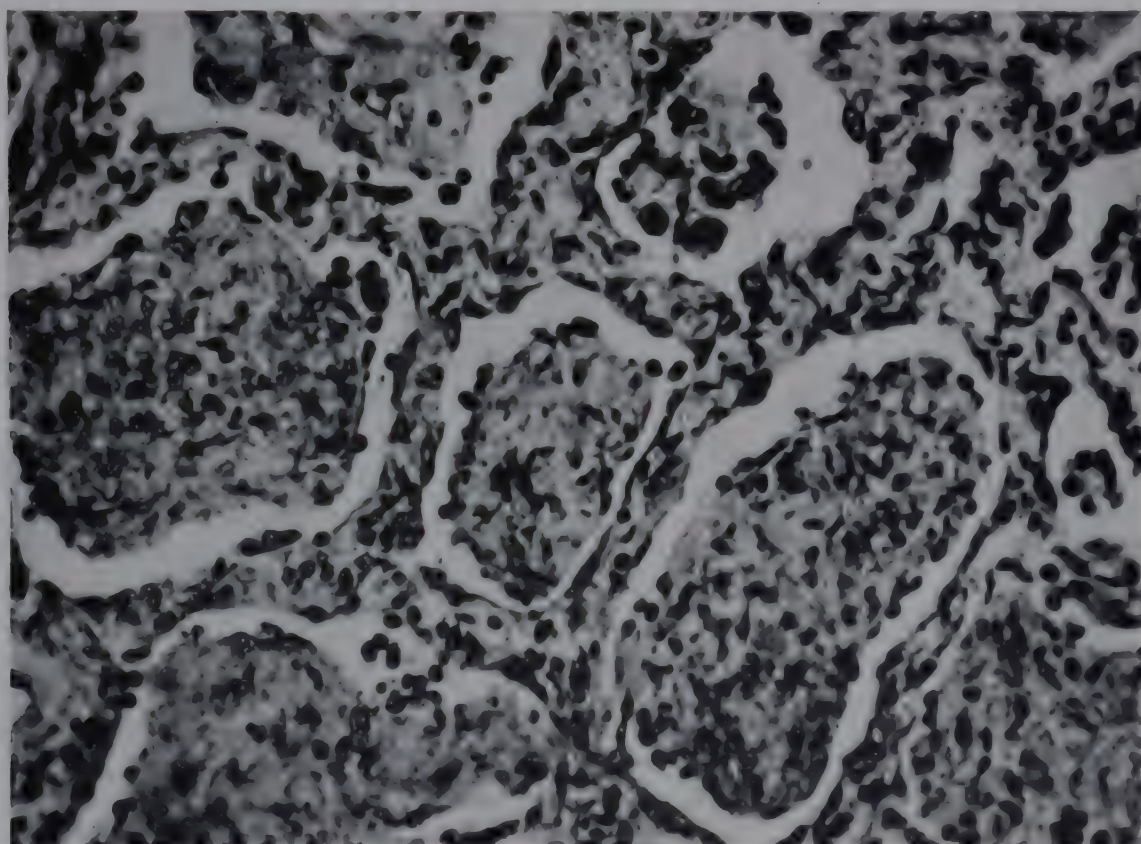


Fig. 190. Pneumonia in Q fever. (Tissue by courtesy of National Institute of Health.)

Varieties of Spotted Fever. There is no essential difference in the clinical course or in the pathologic changes in the eastern and western varieties of the disease, and these designations should not be used. São Paulo typhus of Brazil and boutonneuse fever of the shores of the Mediterranean are varieties of spotted fever.

Tick Bite Fevers. Throughout the world there is a group of diseases apparently transmitted by arthropods, usually ticks, which includes South African tick fever, Kenya typhus, and Colombian spotted fever. There is no agglutination against *Proteus vulgaris* OX-19, OX-K, and OX-2. The methods usually successful in the isolation of bacteria, rickettsiae, and viruses fail to demonstrate the causal agent. Because of the mild character of the

and called "*Rickettsia diaporica*" (Davis and Cox). Further study showed that this organism produced a distinctive disease in Montana known as "Nine-Mile fever," because it was first observed along Nine-Mile Creek. During the spring of 1940, 15 cases of pneumonitis occurred among the 153 employees in one building of the National Institute of Health in Washington, D. C. From these patients *Rickettsia diaporica* was isolated (Dyer, Topping, and Bengtson). It was suspected, and subsequently proved by immunologic methods, that this pneumonitis, Nine-Mile fever, and Australian Q fever were identical (Burnet and Freeman; Dyer).

Pathologic Anatomy. The limited experience with the disease and the few autopsies available render any conclusions concerning

the pathologic anatomy tentative. In the lungs there are congestion and edema and irregular bronchopneumonia. The spleen is enlarged and soft. The remaining organs are essentially normal. The bronchopneumonia is characterized by large amounts of fibrin and infiltration with lymphocytes, plasma cells, and large mononuclear cells. Hemorrhage is conspicuous, but polymorphonuclear leukocytes are few. The cells of the exudate are frequently pyknotic, and organization of the exudate is a prominent feature. The alveolar epithelium is swollen, and the cells tend to a cuboidal type.

Clinicopathologic Correlation. The remarkable feature of Q fever is that there is no correlation between the pathologic lesions in the lung and the clinical signs and symptoms. Despite a definite pneumonitis as shown by x-ray and by autopsy, there is no respiratory difficulty, the respiratory rate is not increased, and usual symptoms of an inflammation of the lung, such as cough, pain, and the production of sputum, are absent or minimal. The mortality rate is low, less than 10 per cent. Agglutination of all strains of *Proteus vulgaris* is negative.

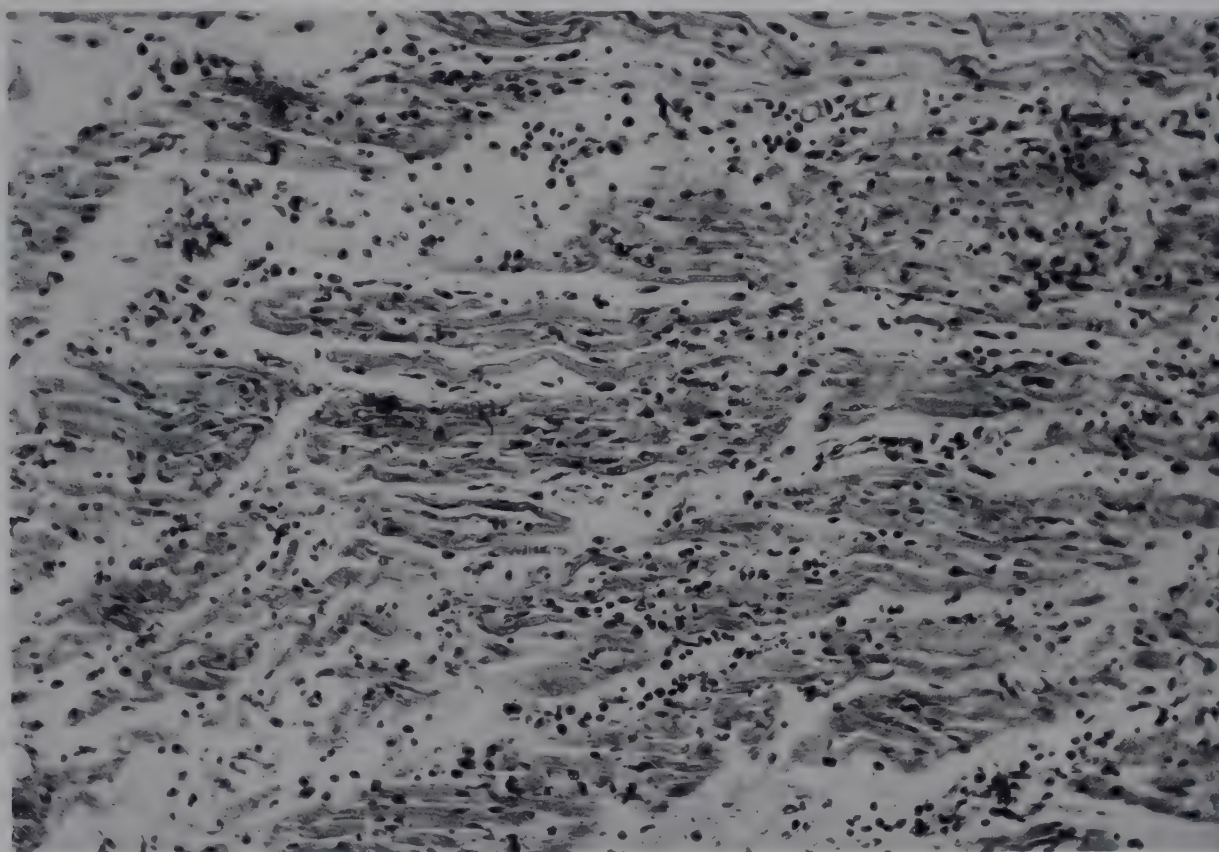


Fig. 191. Acute interstitial myocarditis in tsutsugamushi disease. (Slide by courtesy of Armed Forces Institute of Pathology.)

The bronchi are filled with an exudate similar to that in the alveoli. The septa are edematous and are infiltrated with cells (Fig. 190). Rickettsiae have not been demonstrated in sections of human tissue (Lillie, Perrin, and Armstrong).

Causal Agent. The rickettsia of Q fever is readily isolated from the blood during the febrile period by intraperitoneal inoculation into male guinea pigs (Dyer, Topping, and Bengtson). By direct injection into the lung of monkeys (*Macaca mulatta*) a pathologic process identical with that in man can be produced.

Transmission. The transmission of Q fever by ticks is not clear in many instances, but in epidemics there is some evidence for insect transmission.

Tsutsugamushi Disease

Throughout the Orient, particularly in Japan, Malaya, the Philippines, and the Dutch East Indies, there is a disease known by a number of different names—tsutsugamushi fever, rural typhus, Sumatran mite fever, pseudotyphus, scrub typhus, and coastal fever of Australia—which is transmitted by the mite, *Trombicula delhiensis*, and other species.

Pathologic Anatomy. At the site of the bite of the mite there is usually a small ulcer (5 to 10 mm. in diameter), characterized by necrosis and little or no cellular reaction. The regional nodes are greatly enlarged and contain foci of necrosis. The heart is dilated and flabby. The interstitial tissue is edematous and infiltrated with lymphocytes and mononuclear

cells. In all lymph nodes there is hyperplasia of mononuclear cells. Sparsely distributed minute arteriolar and capillary lesions typical of rickettsial disease are observed. Glial nodules are present in the brain. A nonspecific bronchopneumonia is seen in most fatal cases. Rickettsiae are demonstrated with difficulty (Allen and Spitz).

Causal Agent and Transmission. Rickettsia tsutsugamushi is pathogenic for mice. The larval form of the mite is the only known vector, and infectiousness is apparently inherited in the insect. The nymphal and adult mites do not feed on animals. Other hosts of the larvae include rats and other domestic and wild animals. The reported high titre for OX-K in rats suggests that this animal may be a reservoir.

Clinicopathologic Correlation. The incubation period is seven to fourteen days. The commonest location of the primary lesion is the scrotal and inguinal region. Aside from general signs of infection, the inflammation of the lungs gives rise to cough, and the myocarditis is responsible for circulatory failure. The rash disappears after three to five days. Agglutination with OX-K becomes positive in the second week of the disease (Blake).

Rickettsialpox

This type of rickettsial infection was first recognized in New York City in 1946. It is characterized by an initial lesion of the skin, followed in about one week by fever, chills, sweats, headache, and backache, and in ten days by a generalized maculopapular and papulovesicular rash.

Pathologic Anatomy. Knowledge of the pathologic changes is limited to the initial lesion and the rash.

The initial lesion is a round, red, firm macule, which after slow growth to a maximum size of 5 to 15 mm. becomes vesiculated in the center. There is an infiltration with lymphocytes, mast cells and a few leukocytes. During involution a central black eschar forms.

The lesions of the rash show dilatation of vessels and heavy perivascular and periglandular infiltration with mast cells and lymphocytes. Some capillaries contain thrombi. The vesicles are intra-epidermal.

Causal Agent. Rickettsia akari may be iso-

lated from the blood of patients by intracerebral inoculation of mice or intraperitoneal inoculations of guinea pigs (Huebner, Stamps, and Armstrong). Complement binding antibodies are demonstrable by the usual techniques.

Transmission. The rodent mite, Allodermanyssus sanguineus, carries the rickettsia from mice to man (Huebner, Jellison, and Pomerantz). The rickettsia has been isolated from the tissues of mice (Huebner, Jellison, and Armstrong).

Clinicopathologic Correlation. The onset of symptoms is sudden and the rash lasts four to seven days. There is a slight leukopenia and relative lymphocytosis (Greenberg, Pellitteri, Klein, and Huebner). Except for low positive titres in a few instances, agglutination with Proteus OX-19, OX-2, and OX-K against serum of convalescents is negative. There is a specific complement-fixation test.

Trench Fever

During World War I a disease known as "trench fever" first appeared among British troops in France in 1915. So far as is known it had not been observed before that time. Among the American troops in France there were a total of 901 cases. There is some evidence that the disease is caused by Rickettsia pediculi, and is transmitted by the body louse. Unless there are complications, it is never fatal, and no accurate description of the pathologic anatomy in man is available.

Recovery is complete in from one to two weeks. It has not been possible to produce a similar disease in animals, but experimental infections in man result from the bites of body lice that have fed on ill persons.

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XLVII

Diseases Caused by Viruses: General Considerations

Viruses are a heterogenous group of disease-producing agents, grouped together because they are smaller than the finest particle resolvable by the usual compound microscope. The pathologic reactions to them are also similar, in that all of them produce some degree of hypertrophy and hyperplasia, necrosis, and inflammation. Beyond these two properties they exhibit among themselves as great differences as between viruses and bacteria, or between bacteria and protozoa.

Species-Specificity of Viruses. Many viral diseases occur in two or more species of animals, or can be transmitted to other animals experimentally. For example, the virus causing the St. Louis type of encephalitis in man will grow and produce pathologic change in the brains of monkeys and mice, and will grow in the testes of mice (Smith). On the other hand there are viruses which are capable of producing disease in only a limited number of animals. The virus of the common cold has so far been found pathogenic only for man and for the chimpanzee (Dochez, Shibley, and Mills). Finally there are viruses which are highly specific. In the early attempts at the transmission of the fowl sarcoma, the filtrable agent was effective only in Plymouth Rock chickens (Rous). After acclimatization for many years it will now produce a tumor in any type of chicken. Similarly the Shope papilloma virus of rabbits will not produce disease in any animal except the rabbit. It is perhaps significant that the viruses causing tumors exhibit the greatest degree of species-specificity.

Tissue-Specificity of Viruses. It was early recognized that some viruses affect particularly the nervous system, and they were termed "neurotropic viruses"; others attacked

particularly the skin, and they were called "dermotropic viruses," while still others affected the viscera and were designated "viscerotropic viruses." In some instances there is an even greater degree of specificity than is implied in these terms. The virus of louping ill, when injected into monkeys, selectively destroys the Purkinje cells in the cerebellum, causing complete necrosis and autolysis. The immediately adjacent granular cells and astrocytes are unaffected (Rivers).

Methods of Invasion of the Body. Viruses probably invade the body in the same general way that bacteria do. Experimentally it has been shown that age has a material influence on the normal defense barriers of the animal organism. When the western strain of equine encephalomyelitis virus is injected into the muscles of fifteen-day old mice, 80 to 90 per cent show signs of encephalitis and only a few exhibit flaccid paralysis. At twenty-one days of age, the ratio is reversed: the majority have flaccid paralysis and an appreciable number are entirely resistant. After the age of one month 90 per cent of all mice are resistant to intramuscular inoculation. On the other hand, mice at all ages are susceptible to direct injection of the virus into the sciatic nerve. It would appear that between the ages of fifteen and thirty days there is an anatomic or physiologic change in the nerves so that the virus cannot enter the nerve.

An interesting phenomenon, somewhat similar to but not identical with that of nonspecific resistance to bacteria in the nose and peritoneal cavity, is the so-called "interference phenomenon." The virus of yellow fever inoculated intraperitoneally in mice usually produces no disease, while the virus of

Rift Valley fever under similar conditions is uniformly fatal. When the two viruses are inoculated simultaneously, or when the virus of yellow fever is inoculated shortly prior to the administration of the virus of Rift Valley fever, death of the animals is delayed and some survive. However, if the virus of yellow fever be inoculated several weeks prior to the second inoculation, there is no protection (Findlay and MacCallum).

Transmission of Viral Diseases. In general, viruses are more labile than bacteria, and thus the transmission of a virus from one person to another requires intimate contact or an intermediate host. Yellow fever is an example of

brane, and margination of basophilic chromatin on the nuclear membrane (Cowdry). Inclusion bodies are also occasionally encountered under conditions in which it is reasonably certain that no viruses are present.

Nature of Inclusion Bodies. Inclusion bodies appear to vary as much in nature as the viruses differ from one another. By histochemical methods it can be shown that nuclear inclusions are devoid of mineral matter and give none of the characteristic chemical reactions for nuclei acid (Cowdry). On the other hand the cytoplasmic inclusions found in fowlpox (bodies of Borrell) may be liberated from the cells of tryptic digestion, and

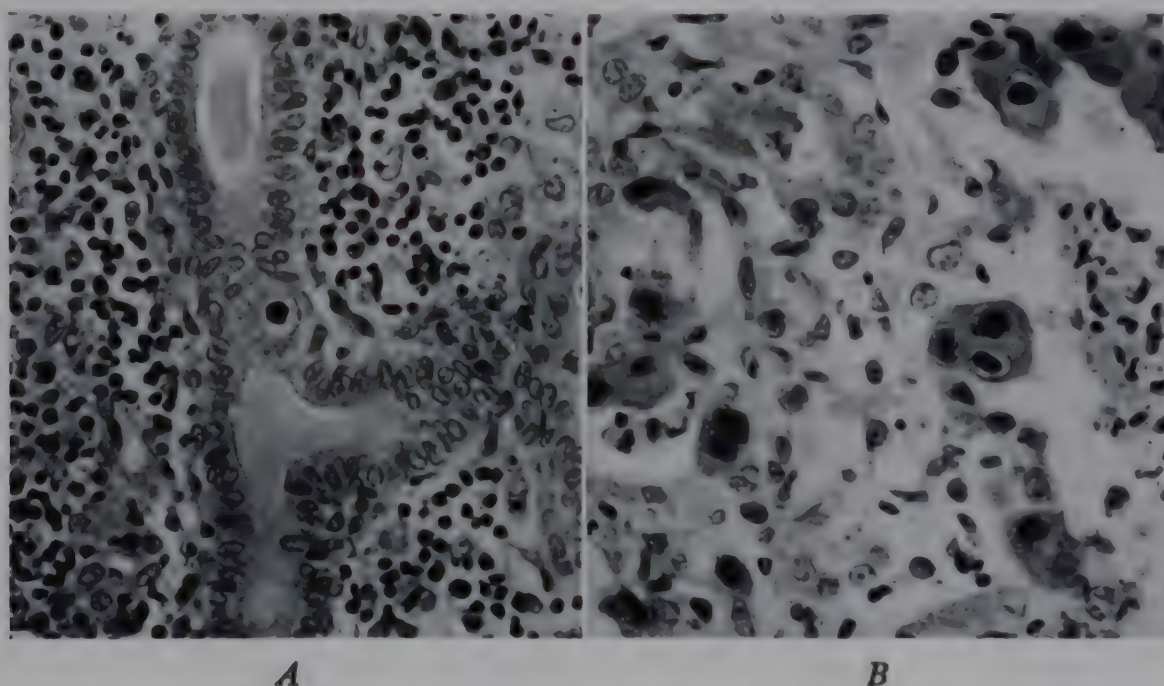


Fig. 192. Intranuclear inclusions. *A*, In the salivary gland. *B*, In the lung. (From tissues studied by McCordock, H. A., and Smith, M. G.: *Am. J. Dis. Child.*)

insect transmission. Evidence has been submitted that the virus of poliomyelitis is present in the sewage from houses and towns in which there is an epidemic, and it is possible that this may be the important mode of spread of this disease (Paul and Trask). The genital sarcoma of the dog probably represents the only disease which has provided for its own transmission, in that the virus is handed down from one animal to another by coitus.

Inclusion Bodies. Histologic study of the affected tissues in most viral diseases reveals the presence of small or large acidophilic bodies in the nuclei or in the cytoplasm, which are termed inclusion bodies and qualified as either *cytoplasmic* or *nuclear*. The principal characteristics of nuclear inclusions are acidophilic staining of the body, presence of a clear halo between it and the nuclear mem-

it would seem that they represent colonies of the virus. The individual bodies are infective for chickens (Woodruff and Goodpasture). In contrast, the cytoplasmic inclusions in the nerve cells in rabies (Negri bodies and lyssa bodies) are undoubtedly the products of the disintegration of neurofibrillae. In the case of the Negri body, the degenerating material collects about the mitochondria, which then represent the central part of the Negri body (Goodpasture).

Saprophytic Viruses—Salivary Gland Virus. In general, the only method for the identification of a virus is the production of disease in man or in the experimental animal. A second, partially reliable method is the demonstration of inclusion bodies within a given organ or cell. In the salivary gland of most adult rats, mice, guinea pigs and moles, cyto-

plasmic inclusion bodies are found in the ductal epithelium. Similar inclusion bodies have been found in about 12 per cent of young children (Farber and Wolbach), and rarely in all of the organs of adults (Von Glahn and Pappenheimer). In the various animals the virus is species-specific, but may be readily transmitted from an old to a young animal. Under certain conditions in mice by massive doses the virus can be made to infect other tissues than the salivary gland (McCordock and Smith).

Humoral Immunity to Viral Diseases. Vaccination. One attack of most viral diseases confers lifetime immunity—e. g., measles, yellow fever, and poliomyelitis. This has been explained by some on the basis of a persistence of the virus in the animal organism. In experimental support of this view, the virus of psittacosis has been recovered from a healthy parrot eighteen months after contact with other parrots; and the virus of encephalomyelitis of mice has been recovered one year after an attack of the disease (Theiler). On the other hand, there are certain viral diseases in which immunity is transient or does not exist at all. After an attack of the common cold, a person is susceptible to another attack within a few weeks or a month. This has been explained on the basis of the lack of invasion of the body and restriction of the infecting agent to nasal cells which are desquamated.

In experimental animals within a few days or a week after the onset of a viral disease there appears in the blood serum a substance which will protect another animal against a lethal dose of the same virus. Substances of this kind are known as neutralizing bodies and are probably not identical with the agglutinins and precipitins and complement-binding bodies of bacterial disease. A great deal of additional investigation is needed for an understanding of the exact relation between neutralizing bodies and susceptibility to viral diseases (Rivers).

Types of Viral Disease. There are many ways to classify viral diseases, but to the pathologist and clinician, the best is a classification based on the type of tissue involved. On this basis there are neurotropic, viscerotropic, and dermatropic viral diseases. Each of these is discussed in the succeeding three chapters.

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XLVIII

Diseases Caused by Viruses: Dermotropic Viral Diseases

The dermotropic viral diseases include among others what are generally referred to as the "infectious exanthemata" or "childhood diseases"—chickenpox, measles, and German measles. In addition there are two diseases of the eye—trachoma and epidemic keratoconjunctivitis.

Vaccinia (Cowpox)

Any one of four types of reaction may follow the introduction of the virus of vaccinia into human skin: vaccinia or primary reaction, vaccinoid or accelerated reaction, reaction of immunity or immediate reaction, and a negative reaction. In the typical vaccinia or primary reaction a small papule appears on the third to fifth day, and is replaced by a vesicle which reaches its greatest development on the eighth to the tenth day or later. In the vaccinoid reaction the papule appears on the third or fourth day, with vesicle formation by the fifth day. The height of the reaction occurs on the sixth or seventh day and rapidly subsides. In the immediate reaction the papule appears within forty-eight hours and subsides without the formation of a vesicle. The first of these reactions indicates complete susceptibility, the second partial immunity, and the third is seen in persons possessing a high degree of immunity. A completely negative reaction indicates not immunity but a technical failure in the vaccination.

Pathologic Anatomy. The pathologic changes: ballooning degeneration of the epithelium, formation of intracytoplasmic inclusion bodies—Guarnieri bodies—and the development of an intra-epithelial vesicle, are identical with the changes in variola. In the

dermis there are edema, congestion, and swelling of the endothelial cells of the capillaries, together with infiltration of mononuclear cells and plasma cells. As in variola, necrosis is associated with infiltration of polymorphonuclear leukocytes.

In the rare fatal case of generalized vaccinia, there are few changes except in the skin. Hyperplasia of lymph nodes and spleen has been reported (Gray).

Causal Agent. The virus of vaccinia is pathogenic for a wide variety of mammals, notably the rabbit and calf. It is readily preserved in glycerin and can be demonstrated by rubbing the glycerinated material into the scarified cornea or skin of a susceptible animal. In all of the experimental lesions there are large numbers of Guarnieri bodies, which probably represent aggregates of minute elementary bodies identical with the virus (Goodpasture). The virus will grow on the chorio-allantoic membrane of the chick embryo and a successful vaccine has been prepared with this material (Goodpasture, Woodruff, and Buddingh). The elementary bodies, also known as "Paschen corpuscles," are agglutinated by specific serum (Ledingham). Chemical analysis of the elementary bodies shows that they are a complex mixture of nucleoprotein and other substances (Hoagland, Lavin, Smadel, and Rivers).

Variola (Smallpox)

Pathologic Anatomy. The gross and microscopic appearances of the lesions of smallpox, especially of those in the skin, depend on the stage of the disease. The initial lesion is a small area of redness on the face. Within twenty-four hours the eruption spreads to all parts of

the body. Within the area of redness a small papule appears, which within a few days changes to a vesicle. On the sixth or seventh day after the appearance of the exanthematous rash, the fluid within the vesicles becomes cloudy, and by the tenth day the vesicles or pustules begin to dry up, unless there are secondary complications. In the so-called "hemorrhagic" smallpox there is hemorrhage into the dermis about the vesicles. In the mucous membranes of the mouth and pharynx there

streptococci or pneumococci, an acute vegetative endocarditis and acute interstitial myocarditis have been reported.

The initial microscopic lesions in the skin are edema, congestion, and infiltration with plasma cells and mononuclear cells in the papillary bodies. The infiltration may be prominent about the capillaries and smaller blood vessels. Within the epithelium of the stratum corneum the cells increase in size and a clear space appears about the nucleus. This



Fig. 193. Smallpox. *A*, Face. *B*, Leg. (Photographs by courtesy of Prof. C. H. Hu.)

may be discrete vesicles and pustules, similar to those on the skin, or a gray necrotic membrane covering the entire tonsillar and pharyngeal region. Occasionally small yellow foci of necrosis and petechiae can be seen in the viscera, especially the liver and adrenals, and in the bone marrow. In the lungs a bronchitis and bronchopneumonia are common, but it is difficult accurately to separate pathologic changes caused by the virus of smallpox from those caused by a secondary streptococcal infection. Rarely small pustules are present in the mucous membrane of the trachea and bronchi. The heart, liver, and kidneys show cloudy swelling, petechiae, and occasionally fatty degeneration. In those cases in which there is a prominent secondary infection with

process is known as "ballooning degeneration" of the epithelium. There follows an infiltration of fluid into the epithelium so that the cells are separated from one another. This fluid contains a small amount of fibrin. Within the cytoplasm or within the area of ballooning degeneration, small roughly spherical inclusion bodies, 1 to 4 microns in diameter, known as "Guarnieri bodies," are found in variable number, although never as abundantly as in experimental variola or vaccinia. With the increased accumulation of fluid within the epithelium, the entrapped epithelial cells undergo necrosis, and a small intra-epithelial vesicle is formed. With the advent of necrosis the epithelium and the fluid of the vesicle are invaded by polymorphonuclear leu-

kocytes and mononuclear cells. With the initiation of healing, the vesicle dries up or ruptures and a crust is formed from the necrotic epithelium of the surface. The cells of the sides proliferate and re-cover this area of skin beneath the crust, which then drops off, leaving a small, depressed, pigmented scar. Scars are more likely to persist on the face than on any other part of the body. The lesions in the mucous membranes are similar to those in the skin, and the necrotic membrane observed is the result of necrosis of the superficial layers

cedure was, however, soon superseded by the methods of Edward Jenner. Jenner observed that farmers in rural England who had had cowpox rarely developed smallpox. The culmination of his investigations was the inoculation of cowpox into a young boy, James Phipps, and the subsequent inoculation of the boy two months later with smallpox, with complete protection from the disease. Medicine owes a great debt of gratitude to two boys, James Phipps and Joseph Meister, in whose bodies the efficacy of vaccination against

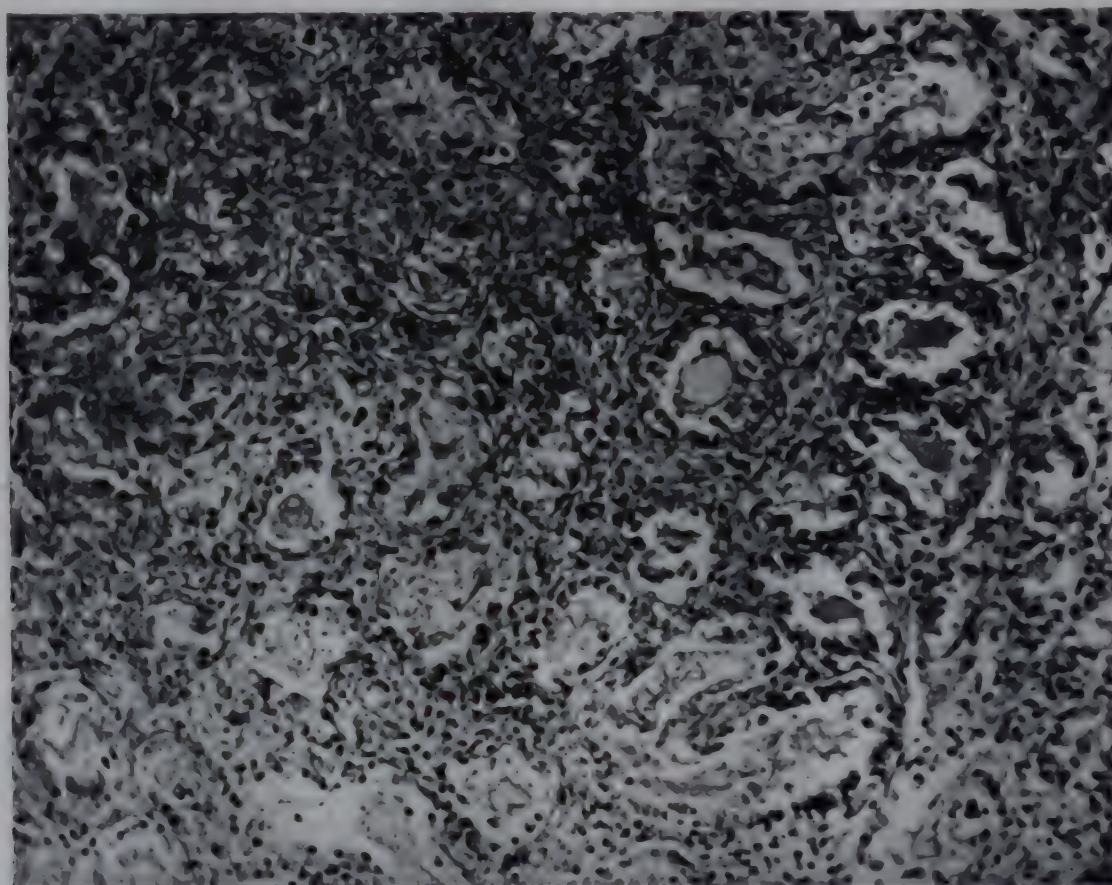


Fig. 194. Lesions in the lung in fetal smallpox. (Tissue by courtesy of Dr. W. E. B. Hall.)

of the epithelium. The small foci of necrosis in the viscera, particularly the testis, and in the bone marrow, appear first as a hyperplasia of endothelial cells, with subsequent necrosis. The lymph nodes show edema, hemorrhage, and hyperplasia of mononuclear cells, but only rarely foci of necrosis. In the kidneys there are interstitial edema and infiltration with mononuclear cells (Michelson and Ikeda; Councilman, Magrath, and Brinckerhoff; Lillie).

Causal Agent. Lady Mary Wortley Montague, on her return from Turkey in the late eighteenth century, first brought to Western Europe the idea that people might be artificially inoculated with smallpox during the course of a mild epidemic, and thus be protected against the severe epidemics, a procedure known as "variolation." This pro-

cedure was, however, soon superseded by the methods of Edward Jenner. Jenner observed that farmers in rural England who had had cowpox rarely developed smallpox. The culmination of his investigations was the inoculation of cowpox into a young boy, James Phipps, and the subsequent inoculation of the boy two months later with smallpox, with complete protection from the disease. Medicine owes a great debt of gratitude to two boys, James Phipps and Joseph Meister, in whose bodies the efficacy of vaccination against smallpox and rabies was first demonstrated. Although one hundred and fifty years have elapsed since this initial demonstration of the cross-immunity between variola and vaccinia, the relation of the two viruses is not yet fully elucidated. It is the general opinion that the two viruses are similar, if not identical, and differ only in the degree of virulence. The experimental demonstration of the virus of smallpox is readily made by what is known as the Paul test. Material from a vesicle or pustule is rubbed into the scarified cornea of the eye of the rabbit. After thirty-six hours there are minute white elevations with a central depression. The animal is sacrificed at the end of forty-eight hours and the cornea is studied grossly and microscopically. Within the epithelial cells large numbers of Guarnieri bodies are easily demonstrated, together with

hyperplasia and ballooning degeneration of the epithelium. The general properties of the virus are discussed in the section on vaccinia. Cross-neutralization tests clearly demonstrate that the virus of variola and the virus of varicella are two distinct entities.

Transmission. In most instances the virus is transmitted by close contact with an ill person through desquamated crusts and the respiratory secretions. However, the ability of the virus to survive in dust and on bed clothing make possible remote secondary infections (Downie and Dumbell). Intra-uterine infections are observed (Fig. 194).

Clinicopathologic Correlation. The incubation period of variola averages twelve days, and this is followed by the general signs and symptoms of invasion by an infectious agent: headache, fever, backache, and gastrointestinal disturbances, all of which may be extremely severe. In from four to six days the rash appears, with some remission of the general symptoms. If fatal secondary infection supervenes, it appears six to seven days after the eruption, and manifests itself as a streptococcal bronchopneumonia or a streptococcal septicemia. Bacterial infection of the pustules on the skin is usually by the staphylococcus (Hines).

Alastrim. In certain parts of the world a disease similar to smallpox has been termed "alastrim." It differs from variola only in the mildness of its course and its low mortality, which does not exceed 2 per cent. Experimental studies to reveal an infectious agent, using methods which have been successful with variola and vaccinia, have failed to show a virus. Further work is necessary before the relation of these two diseases can be stated with certainty (MacCallum and Moody).

Varicella (Chickenpox)

Pathologic Anatomy. The initial lesion in varicella is a small macule, which disappears on pressure. Within a few hours this is replaced by a papule, and later by a small vesicle. The vesicles are surrounded by narrow hyperemic zones. All of the lesions do not go on to the formation of a vesicle. The rash first appears on the face and back, and then spreads to the rest of the body. The initial microscopic change consists of the appearance of acidophilic intranuclear and in-

tracytoplasmic inclusion bodies in the cells of the stratum corneum. Within a short time the cells enlarge and the nucleus undergoes amitotic division, so that epithelial cells with from six to eight nuclei are not uncommon. The dermis immediately beneath the rash shows congestion, edema, and infiltration with mononuclear cells and lymphocytes. The vesicle is formed within the epithelium by an intercellular edema which gradually increases and splits the cells apart until a uniloculated or multiloculated cavity is produced. The fluid within the vesicles contains a small amount of fibrin and occasional mononuclear cells. There is rarely infiltration with polymorphonuclear leukocytes.

Repair is brought about by the usual process of the healing of a vesicle. The fluid coagulates or the vesicle ruptures, a crust is formed on the surface, and the epithelial cells at the edge proliferate beneath the crust, which drops off. Similar lesions of the epithelial cells making up the hair follicles may be observed. Nothing is known concerning any associated changes in the internal viscera, since patients practically never die of uncomplicated varicella (Tyzzer).

Causal Agent. The virus of varicella may be recovered from the fluid within the vesicles and from the blood during the first twenty-four to forty-eight hours. On injection into the testes of rabbits and of African vervets (*Lasiopyga pygerythra*), intranuclear inclusions are formed similar to those observed in the skin of man. The virus may be passed serially in the testis, and after a time will produce lesions on direct inoculation of the skin and of the cornea (Rivers and Tillett). By cross-neutralization tests it can be shown that the virus of varicella is different from the viruses of variola and vaccinia. For many years individual examples have been reported of what appears to be contraction of varicella from a patient with herpes. The answer to this problem must await further investigation, but statistical and cross-neutralization tests would indicate that the two viruses are separate and distinct entities in most cases (Rivers and Eldridge).

Transmission. Varicella is transmitted from child to child by direct contact, either through the lesions on the skin or through the secretions of the upper respiratory tract.

Clinicopathologic Correlation. The incuba-

tion period averages fourteen days. The general symptoms of infection in varicella are slight, or may be entirely absent. A fever rarely lasts for more than one or two days. There may be a slight coryza and rhinitis in association with the more obvious rash on the skin. Secondary infection with streptococci has been reported, and encephalitis beginning on the fourth to eighth day is a rare, but usually not fatal, complication. The patho-

and is pathogenic for monkeys. Transmission is largely by direct contact during the infective period which is from one to two days before the rash appears to the end of the febrile period.

Clinicopathologic Correlation. The incubation period is fourteen to twenty-one days. All symptoms are mild. The only serious complications are an encephalitis of the postinfectious type and purpura (Ginsberg and Wilson).



A

B

Fig. 195. *A*, Chickenpox with pleomorphic lesions on hand and thigh. (Photograph taken by Dr. Malcolm Cook.) *B*, Measles. Note the macular lesions (more abundant on the face), the conjunctivitis, and the edematous eyelids. (Photograph taken by Dr. Malcolm Cook.)

logic changes are similar to those of other types of postinfectious encephalitis and they are discussed in a separate section (p. 937).

Rubella (German Measles)

Rubella (Rötheln or German measles) is characterized by mild constitutional symptoms and eruption, and enlargement of lymph nodes, particularly those of the posterior cervical chain (Wesselhoeft).

Pathologic Anatomy. Histologic studies of the skin are not adequate. The lymph nodes are hyperplastic.

Causal Agent and Transmission. The virus of rubella is present in nasopharyngeal secretions, grows on the chorio-allantoic membrane

There is a leukopenia and relative lymphocytosis (MacBryde and Charles).

Relation to Congenital Anomalies. The original observations of Gregg that infants born of mothers who had rubella during the first trimester of pregnancy are likely to have congenital anomalies has been confirmed by many studies. The most common lesions are anomalies of the heart, deaf-mutism, microcephaly, and cataracts (Swan, Tostevin, and Black).

Rubeola (Measles)

The characteristic visible external sign of measles is an erythematous rash over the skin, together with the formation in the mouth of

small, grayish yellow spots with red haloes, known as "Koplik's spots."

Pathologic Anatomy. Histologic examination of the lesions on the skin shows slight to moderate edema, congestion, and infiltration of lymphocytes and mononuclear cells in the dermis. In the more severe cases there is also hemorrhage into the interstitial tissue. Within the epidermis small foci of fluid accumulate, with secondary necrosis of the epithelial cells. The cells first show perinuclear, vacuolar degeneration, and then undergo hyaline necrosis.

the exanthematous rash: in the subepithelial tissue of the tonsil and even within the epithelium, large multinucleated giant cells are formed. These cells contain from six to twenty closely packed nuclei. There is an associated infiltration with lymphocytes and monocytes (Warthin). Similar changes are found in the larynx and trachea (Semsroth). In the lung in fatal cases there is a bronchopneumonia similar in all respects to that which follows influenza, described by MacCallum as interstitial bronchopneumonia. *Streptococcus hae-*

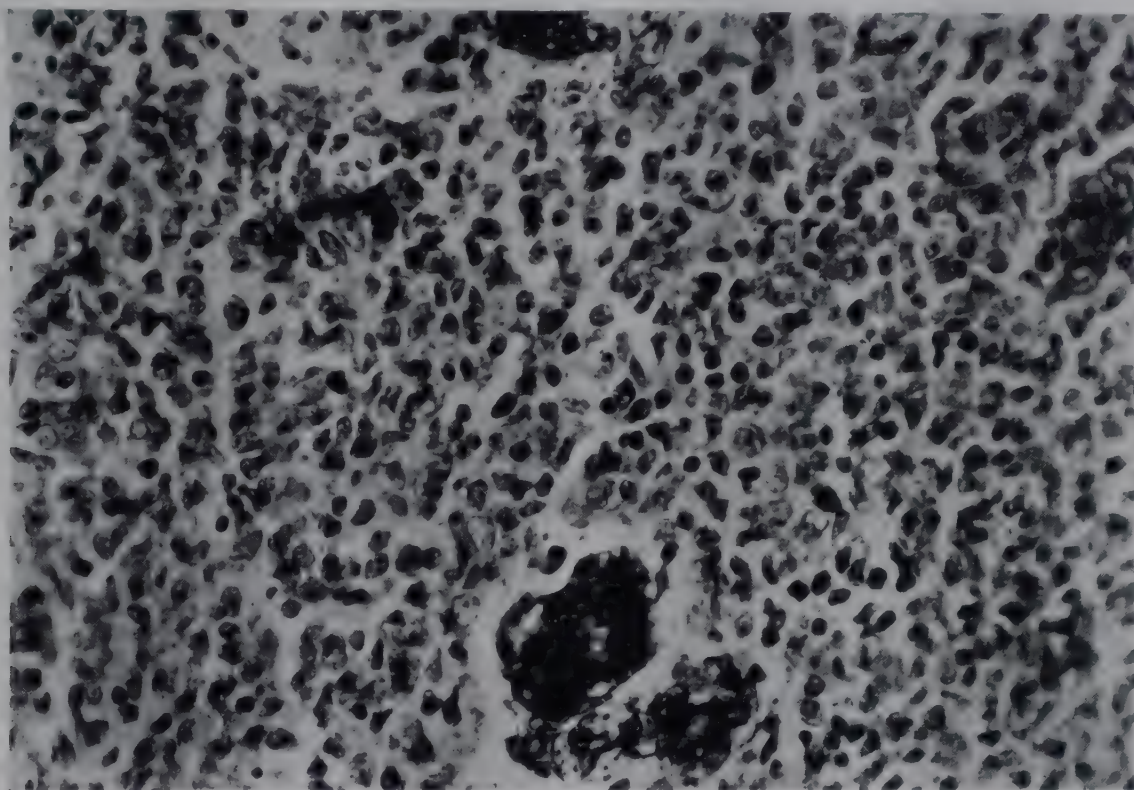


Fig. 196. Giant cells in the lymphoid tissue of the appendix in measles. (Tissue by courtesy of Dr. Paul Wheeler.)

Some of the monocytes in the adjacent dermis are filled with vacuoles of fat. There is hyperkeratosis of the superficial layers of the epidermis. The endothelial cells of the small capillaries are swollen and occasionally show mitoses (Ewing). Microscopic examination of the Koplik spot reveals an infiltration of polymorphonuclear leukocytes about the submucous glands, with dilatation of capillaries, and hemorrhage in the surrounding tissue (Fig. 196, p. 375).

In the pharynx, larynx, trachea, and bronchi, it is difficult to distinguish between the pathologic changes caused by the virus of measles and those caused by secondary infection with streptococci, which is so common in the fatal cases. One change is clearly caused by the virus, since it occurs during the prodromal stage, from one to four days before

molyticus can be isolated from the lungs and is present in sections in large numbers.

All the lymph nodes of the body are enlarged, soft, and congested. The spleen is the seat of an acute hyperplasia. Occasionally, there are small foci of necrosis in the liver and spleen. An encephalitis characterized by perivascular lymphocytic infiltration, degenerative changes in nerve cells, and perivascular demyelination may occur at any stage in the disease (Appelbaum, Dolgopol, and Dolgin).

Causal Agent. The blood and nasal washings of children during the first days of the disease, when filtered, will produce an identical disease in monkeys (Shaffer, Rake, Stokes, and O'Neil). Giant cells, similar to those in man, are present in the lymph nodes of the monkeys (Gordon and Knighton). The condition in monkeys may be serially trans-

ferred, and material inoculated onto the chorio-allantoic membrane of the chick embryo will similarly produce disease in monkeys and in man. No gross lesions develop on the chick membrane.

Transmission. The virus of measles is probably passed directly from child to child through the secretions of the nose and mouth. A person is infective for several days before the rash appears.

Clinicopathologic Correlation. The clinical signs and symptoms of uncomplicated measles are slight. There are a mild cough from the inflammation of the upper respiratory tract, an increased secretion of mucus from the nasal mucosa resulting from the inflammation in that area, and usually a slight inflammation of the eyes. The rash is usually not troublesome. In severe cases of measles there is often a secondary streptococcal bronchopneumonia, which occasionally is fatal. This pneumonia is of the interstitial type and produces the intense dyspnea and cyanosis characteristic of this variety of pneumonia. The incubation period of measles averages ten or eleven days, and this is followed by the stage of invasion of three to four days. The explosive epidemicity of measles is well shown when the disease is introduced into a community which for centuries has been free of it. In the Faeroe islands in 1846 there were 6000 cases in a total population of 7782.

Herpes Simplex

Herpes simplex, better known as a fever blister, occurs most frequently on the lips and on the genitalia, but may be found on any part of the face or on the conjunctiva. It appears first as a small patch of erythema, which changes to a thin-walled vesicle filled with clear fluid.

Pathologic Anatomy. Microscopic section of the fully developed vesicle shows a heavy infiltration of polymorphonuclear leukocytes in the corium beneath and about the vesicle. There is an associated edema and congestion. The vesicle forms within the epithelium in essentially the same way as the vesicles of varicella. In the epithelial cells about the vesicles there are typical intranuclear inclusions (Lauda and Rezek).

Causal Agent. The virus of herpes simplex is present in the fluid of the vesicles, and con-

junctivitis is readily produced by the inoculation of the scarified cornea of the rabbit (Goodpasture and Teague). In the cornea there are typical intranuclear inclusions. Certain strains of the herpetic virus are neurotropic, and following inoculation into the masseter muscle there are demonstrable changes in the motor nucleus of the fifth cranial nerve.

Transmission. Although the virus of herpes simplex may be transferred from person to person by intimate contact, such as kissing, most cases of the disease probably arise from a virus carried in the normal skin and nerve tissue. This is supported by the observation that about 50 per cent of persons subjected to fever therapy acquire herpes on the lips (Warren, Carpenter, and Boak). The herpetic virus may occasionally be recovered from normal brain tissue (Flexner and Amoss).

Clinicopathologic Correlation. Herpes simplex is usually not a primary disease but is found in association with any disease in which there is an increase in temperature. The reason for this predisposing factor for the action of the virus is not clear. Aside from the slight itching, the local lesions of herpes bring about little inconvenience. It is supposed that this itching is caused by slight irritation of the sensory nerves to that area. In a few patients there is an associated syndrome suggesting encephalitis, and in a rare case there is a true encephalitis with death (Smith, Lennette, and Reames).

Herpetic or Aphthous Stomatitis and Pharyngitis. Particularly in children, but also in adults, there is a peculiar type of inflammation of the mouth and pharynx characterized by the appearance of red blisters on the mucous membrane, which become ulcerated and covered by a yellowish white membrane. The intra-oral lesions are not infrequently associated with herpes of the lips. From these lesions a virus can be secured which is identical with that of herpes (Scott and Steigman).

Trachoma

Pathologic Anatomy. It is customary to describe trachoma in three stages: the period of onset, the hypertrophic stage, and the cicatricial stage. The first pathologic change is an acute catarrhal conjunctivitis, followed in from seven to ten days by the appearance of

numerous small follicles in the conjunctiva. These follicles are minute, red or yellow elevations on an intensely hyperemic mucous membrane. In the hypertrophic stage the follicles enlarge and come to involve practically all of the palpebral and retrotarsal conjunctiva. From the upper limbus a vascularized white membrane grows down as a pannus over the cornea. In the cicatricial stage gray or white scars appear in the conjunctiva and increase as the follicles gradually disappear. The pan-

can be secured if the material is emulsified and filtered. The incubation period in the monkey varies from a few days to a month, and the cornea is never involved. Inclusion bodies are found, but they cannot be directly related to the infectivity of the material. In from a few weeks to a year the lesion completely heals and there is no resistance against a subsequent infection (Julianelle and Harrison).

Transmission. The virus is spread from person to person by close personal contact. The

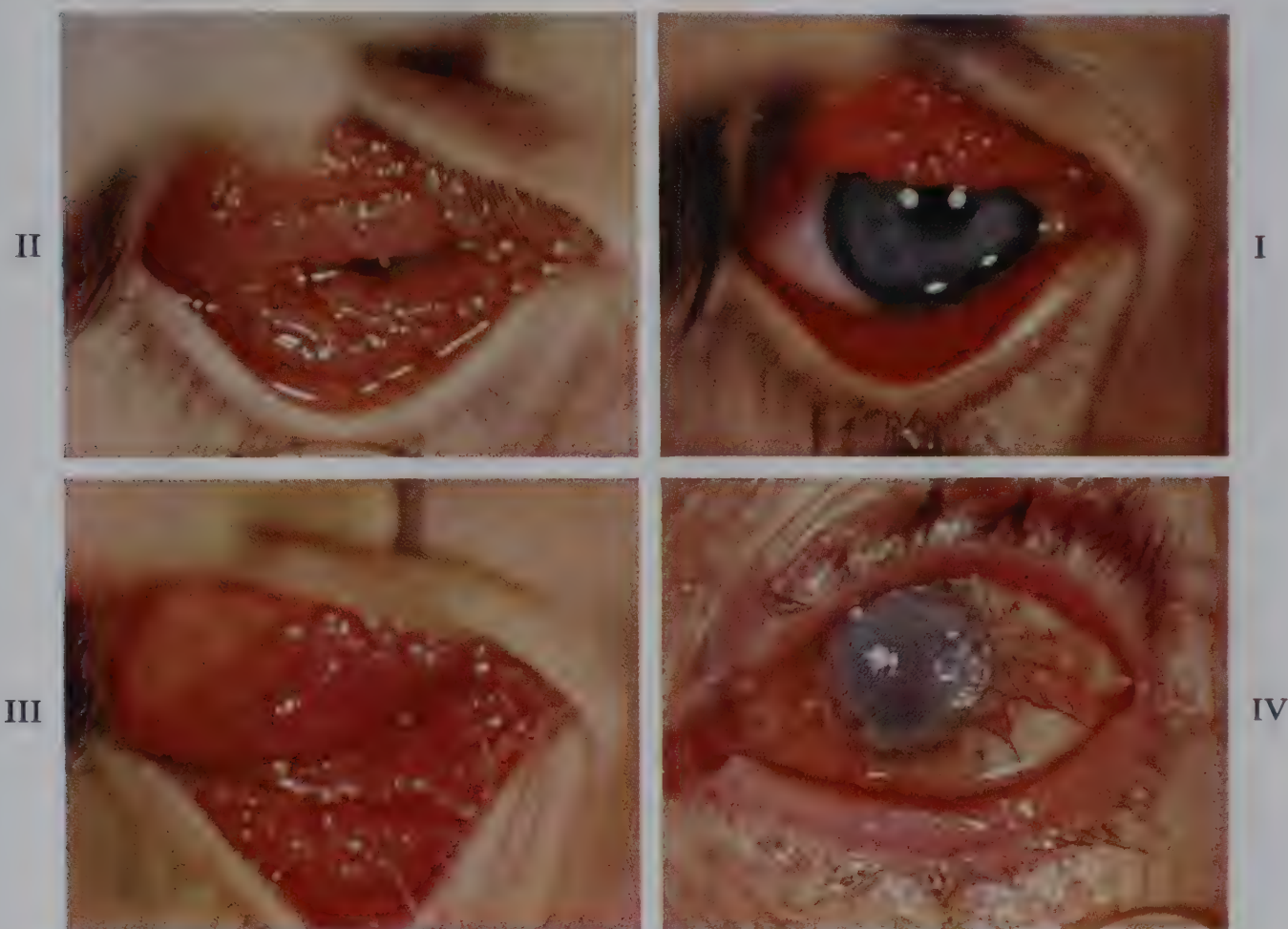


Fig. 197. Four stages in the development of trachoma. (Photographs by courtesy of Dr. Lawrence Post.)

nus continues to grow from all sides over the surface of the cornea. A fourth or healed stage may be observed following mild or abortive cases. In early stages there are edema and hyperemia, and the follicles are composed of focal accumulations of lymphocytes and plasma cells. The epithelium of the conjunctiva contains small inclusion bodies which are characteristic, and which when observed in scrapings may be used to establish the diagnosis.

Causal Agent. The virus of trachoma is difficult to demonstrate and cannot be carried serially in experimental animals. If the scrapings from a trachomatous eye are swabbed into the eye of the monkey, lesions identical with those in man will develop. Similar results

disease is common in Egypt and Palestine, where approximately 90 per cent of the native population is affected. In the United States it is widespread among the Indians and in certain localities of Tennessee, Kentucky, and Missouri.

Clinicopathologic Correlation. The formation of a scar in the upper lid leads to entropion and irritation of the cornea by the eyelashes. Involvement of the levator muscle may produce ptosis. The inflammation during the first and second stages is associated with pain and photophobia. Growth of the pannus eventually leads to blindness.

Inclusion Blennorrhea and Swimming-bath Conjunctivitis. These two diseases of the eye are probably caused by a virus similar to, but

not identical with, the virus of trachoma. Both diseases can be transmitted to monkeys, but since no immunity develops, it is impossible to demonstrate the relation of the viruses. The gross lesions and microscopic appearance are similar to those of trachoma, but differ in that they are less severe and heal spontaneously in man (Julianelle; Julianelle, Harrison, and Lange).

Epidemic Keratoconjunctivitis

Although known for many years this specific type of keratoconjunctivitis first attained importance during World War II.

tion. The serum of a recovered patient contains neutralizing bodies.

Clinicopathologic Correlation. Systemic symptoms are not conspicuous, and consist of headache, fever, and general malaise. The duration varies from one to eight weeks, and in some persons there is permanent impairment of vision up to 15 per cent. Although the disease is highly contagious and occurs in epidemic form, there are certain individual predisposing factors. In many instances it develops subsequent to ocular trauma or non-specific inflammations (Sanders, Gulliver, Forchheimer, and Alexander; Sanders and Alexander).

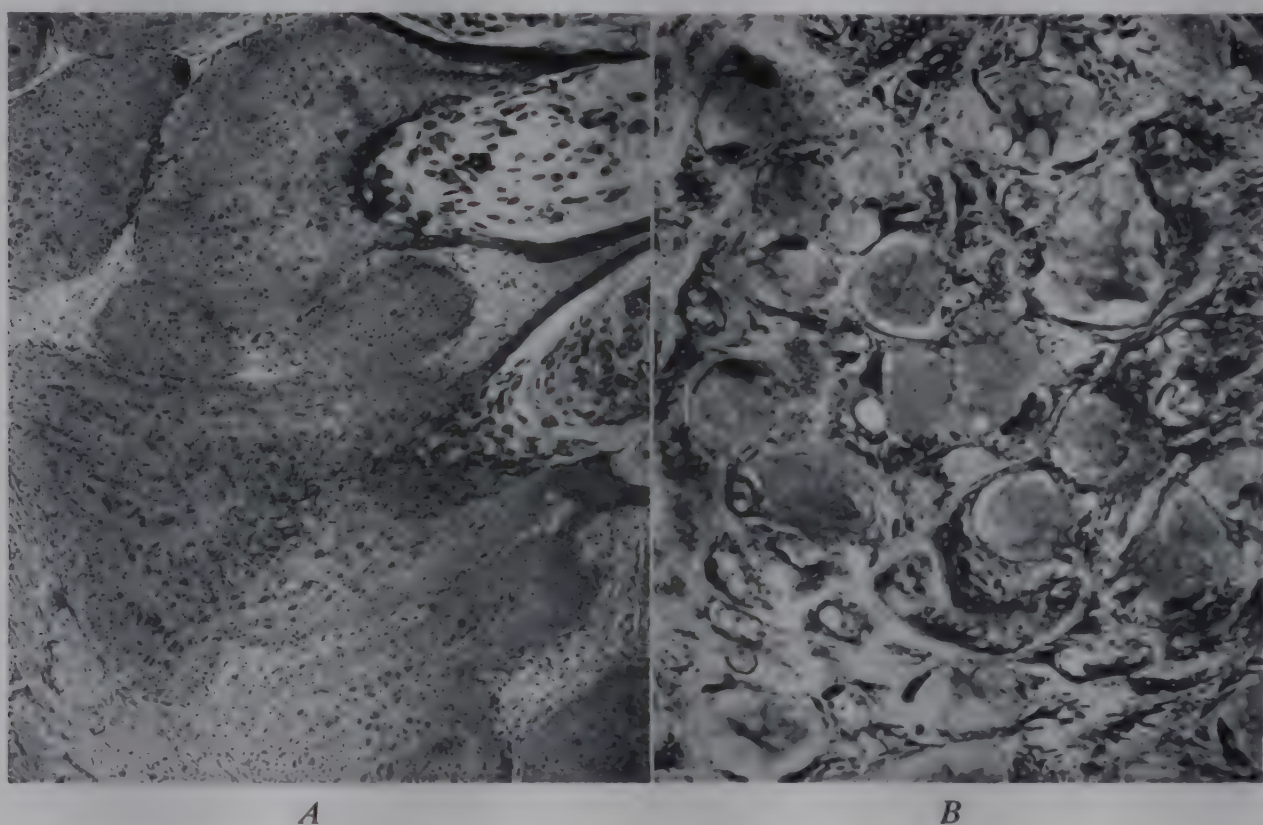


Fig. 198. Molluscum contagiosum. *A*, Low power to show the hyperplasia of the epidermis. *B*, High power to show the molluscum bodies.

Pathologic Anatomy. It is characterized by hyperemia and swelling of the palpebral conjunctiva. After from twelve to thirty-six hours the bulbar conjunctiva is hyperemic, and there is often conspicuous edema of the lids. There is no discharge, but in scrapings the predominant cells are the lymphocyte and the mononuclear leukocyte. The preauricular lymph nodes are regularly enlarged, and the submaxillary and cervical lymph nodes occasionally enlarged. In about half of patients there is focal infiltration and opacity of the cornea.

Causal Agent. Tissue cultures inoculated with the scrapings from the palpebral conjunctiva are after the tenth day of the disease pathogenic for mice on intracerebral inocula-

Molluscum Contagiosum

Pathologic Anatomy. The well-developed lesion of molluscum contagiosum is a small, firm papule, 2 mm. in diameter, in the epidermis, with a minute, round orifice at its apex, through which a pearly white central core may be seen. The surrounding tissue is normal. The cells of the germinal layer of the epithelium are large and show numerous mitoses. The cells and the nuclei of the stratum corneum immediately adjacent to the basal layer are enlarged and the nuclei are prominent and often vacuolated. Nucleoli in the process of extrusion from the nucleus are readily observed, and the cytoplasm about

these extruded nucleoli tends to be basophilic. In the more peripheral portion of the cytoplasm of the cells there are vacuoles, and about the vacuoles there is an abundant, finely granular material which stains pink with acid fuchsin. In the larger vacuoles these minute discrete granules—bodies of Lipschütz—completely fill the space. With continued growth of the elementary bodies the cytoplasm and the nucleus are pushed to one side of the cell (Fig. 198), and under low power the cell appears to be occupied by a large hyaline mass known as a molluscum body, made up of fused, desiccated, elementary bodies and the intervening cytoplasm (Goodpasture and King).

Causal Agent. The virus of molluscum contagiosum is pathogenic for man only, and experimental lesions have been produced by inoculation of a filtrate (Wile and Kingery). Tryptic digestion will release the molluscum bodies, and trituration reveals that they are composed of innumerable small elementary bodies which are the virus (Goodpasture and Woodruff).

Transmission. The natural disease is probably transferred by intimate contact between two persons, or by auto-inoculation with the fingers.

Clinicopathologic Correlation. There is no general invasion of the body, and clinical signs and symptoms are limited to the appearance of the small nodules on the surface of the skin.

Foot and Mouth Disease

Foot and mouth disease is a highly infectious disease of cloven-footed animals. It is rarely contracted by man from ingestion of virus-contaminated food or contact with diseased animals.

After an incubation period of two to eighteen days the symptoms and signs are fever, salivation, and vesicles in the buccal cavity and on the skin of the soles, palms, digits, and interdigital areas. The vesicles are intra-epidermal and intranuclear inclusions are present in the epithelial cells. There is infiltration with leukocytes in the adjacent connective tissue.

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XLIX

Diseases Caused by Viruses: Viscerotropic Viral Diseases

The diseases caused by viruses in which the principal pathologic changes are in the abdominal and thoracic viscera include among others some of the major epidemic diseases of man: yellow fever, influenza, infectious and serum hepatitis, mumps, psittacosis, and dengue. One disease of the group—venereal lymphopathy—has been discussed in the section on venereal diseases (page 349).

Yellow Fever

Pathologic Anatomy. Although there are pathologic changes in most of the viscera in fatal cases of yellow fever, the principal change is in the liver. The liver is normal in size and reddish gray or yellowish gray in color, and on section the parenchyma bulges from beneath the capsule. Beneath the capsule or within the substance there are occasional petechiae. On the cut section the lobular architecture is partially obscured, but no focal areas of necrosis are discernible except with a hand lens. The characteristic microscopic change is necrosis, affecting the midzonal region of each hepatic lobule. Within this area there are fatty degeneration and cloudy swelling in the cytoplasm, and karyolysis and karyorrhexis of the nuclei. Within the cytoplasm there are focal areas of hyaline necrosis, with granules and vacuoles within them, known as "Councilman's lesions." In about one-third of human cases there are characteristic multiple, small, intranuclear inclusion bodies (Cowdry and Kitchen). In the remaining hepatic substance there is depletion of glycogen. The Kupffer cells are unchanged, and there is no evidence of transudation of fluid or migration of cells, except in a rare

case (Klotz and Belt). According to experienced observers, this lesion has never been seen in any other disease except in an occasional severe burn (Belt).

The spleen is normal in size, soft and dark red. Malpighian bodies are indistinct. Microscopically, depletion of the lymphoid tissue and slight hyperplasia of the endothelial cells about the follicles are noted (Klotz and Simpson). The heart is pale and shows advanced fatty degeneration (Cannell). In the brain there are small foci of perivascular hemorrhage and occasional perivascular lymphocytic infiltration, particularly in the subthalamie regions about the third ventricle (Stevenson). The kidneys are slightly enlarged and pale. Microscopically all grades of cloudy swelling, fatty degeneration, and necrosis of the epithelium of the proximal convoluted tubules are seen. In the mucosa of the gastro-intestinal tract, throughout many of the viscera, and in the skin, there are petechiae and ecchymoses. The lumen of the gastro-intestinal tract is partially filled with dark blood. The lymph nodes, particularly in the abdomen, are enlarged, and microscopically may show small foci of necrosis. The adrenal glands are congested and small areas of hemorrhage and necrosis may be seen microscopically. The degree of generalized jaundice is variable and is shown best at autopsy in cartilage and in the intima of the aorta.

Causal Agent. The subcutaneous inoculation into *Macacus rhesus* monkeys of citrated blood from a person with yellow fever during the first few days of the disease, reproduces a disease identical with that in man. The monkey may also be infected by the bite of the mosquito (Stokes, Bauer, and Hudson). In-

tracerebral inoculation into mice brings about a rapidly fatal encephalomyelitis. If the virus mixed with immune serum is injected intraperitoneally, and starch is injected intracerebrally, mice are protected. This is the method routinely used for the testing of the immunity of large groups of people (Sawyer and Lloyd). The virus can be cultivated in minced mammalian embryos and under these conditions loses its pathogenicity for monkeys and for man, but retains its antigenicity (Theiler and Smith). This living culture virus has been successfully used for the vaccination of man (Soper and Smith).

cities of Central and South America, yellow fever became rarer. But with further study new discoveries were made which upset the simple theory of the transmission of yellow fever from man to man by the aegypti mosquito. It was found that yellow fever existed in certain regions of South America where there were no aegypti mosquitoes. At about the same time, the virus was discovered; neutralization tests for immunity were developed; and a procedure for removal of a small piece of liver with a viscerotome was made possible. Investigations with these three new tools confirmed the clinical observation that yellow

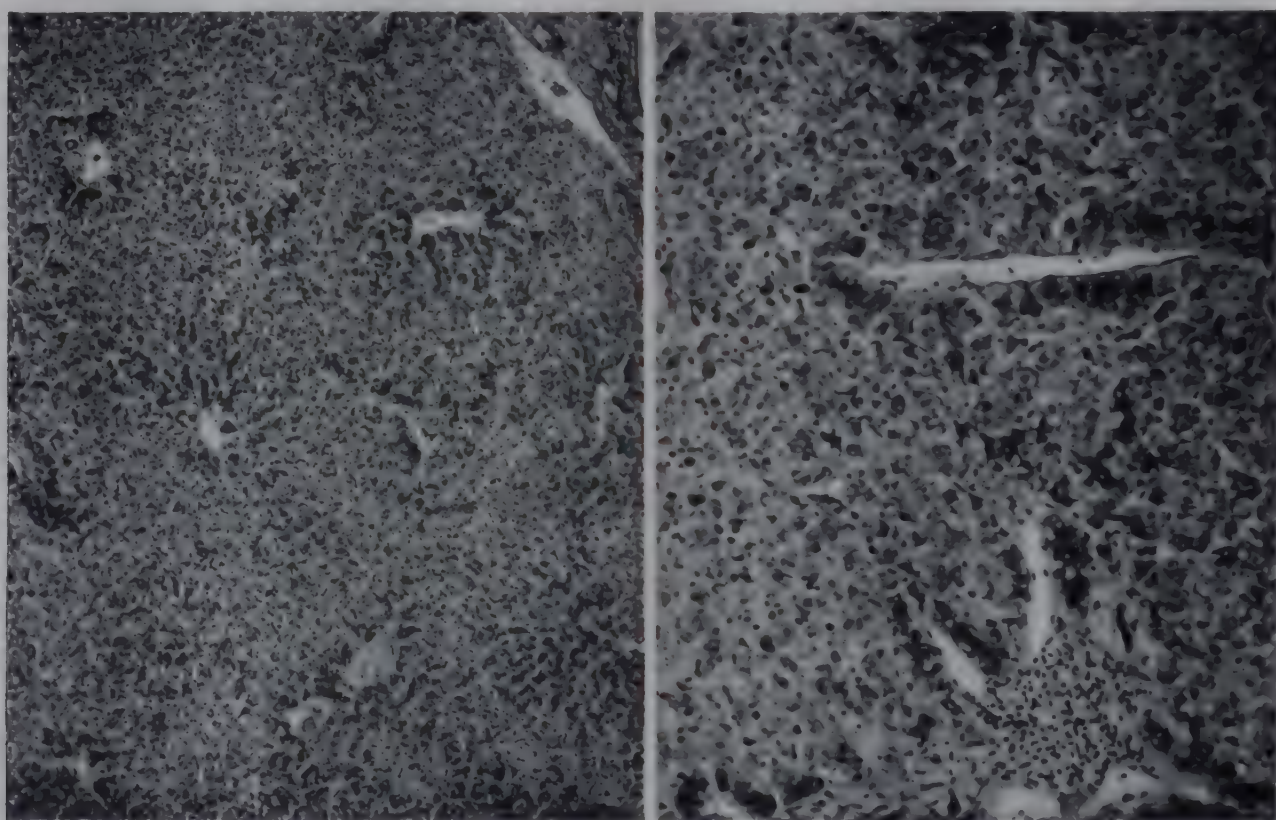


Fig. 199. Midzonal necrosis of the liver in yellow fever. (Tissue by courtesy of Armed Forces Institute of Pathology, Acc. No. 29730.)

Transmission. The brilliant investigations of the Yellow Fever Commission of the United States Army in Cuba laid the foundation for our present knowledge of yellow fever (Reed, Carroll, and Agramonte). Briefly, Walter Reed and his associates found that the female mosquito, *Aedes aegypti*, when allowed to feed on a patient with yellow fever, was able to transmit this disease by its bite to another person after some twelve days. Hence it appeared that the control of yellow fever was largely a matter of the control of mosquitoes, and the monumental work of Gorgas and others during the succeeding twenty years bore out this statement. When the breeding places of mosquitoes were controlled in the

fever existed as a definite endemic disease in the jungles of Brazil. This type of yellow fever, not transmitted by the aegypti mosquito, is known as "jungle yellow fever." Tests on wild animals showed that yellow fever was prevalent among many of them, particularly monkeys, and the conviction is growing that animals are the natural reservoir of the virus of yellow fever, and that the transmission of the disease by the aegypti mosquito to man, and from man to man is accidental. These discoveries have reopened the entire problem of epidemicity and control of yellow fever. The rapid development of aviation has posed another problem in mosquito control: today an airplane can, in twenty-four hours, carry an

infected mosquito from the tropics to Florida, and thus possibly initiate an epidemic in North America.

ing. The severe pathologic changes in the liver account for the abdominal tenderness and the jaundice. The necrotizing lesion of the

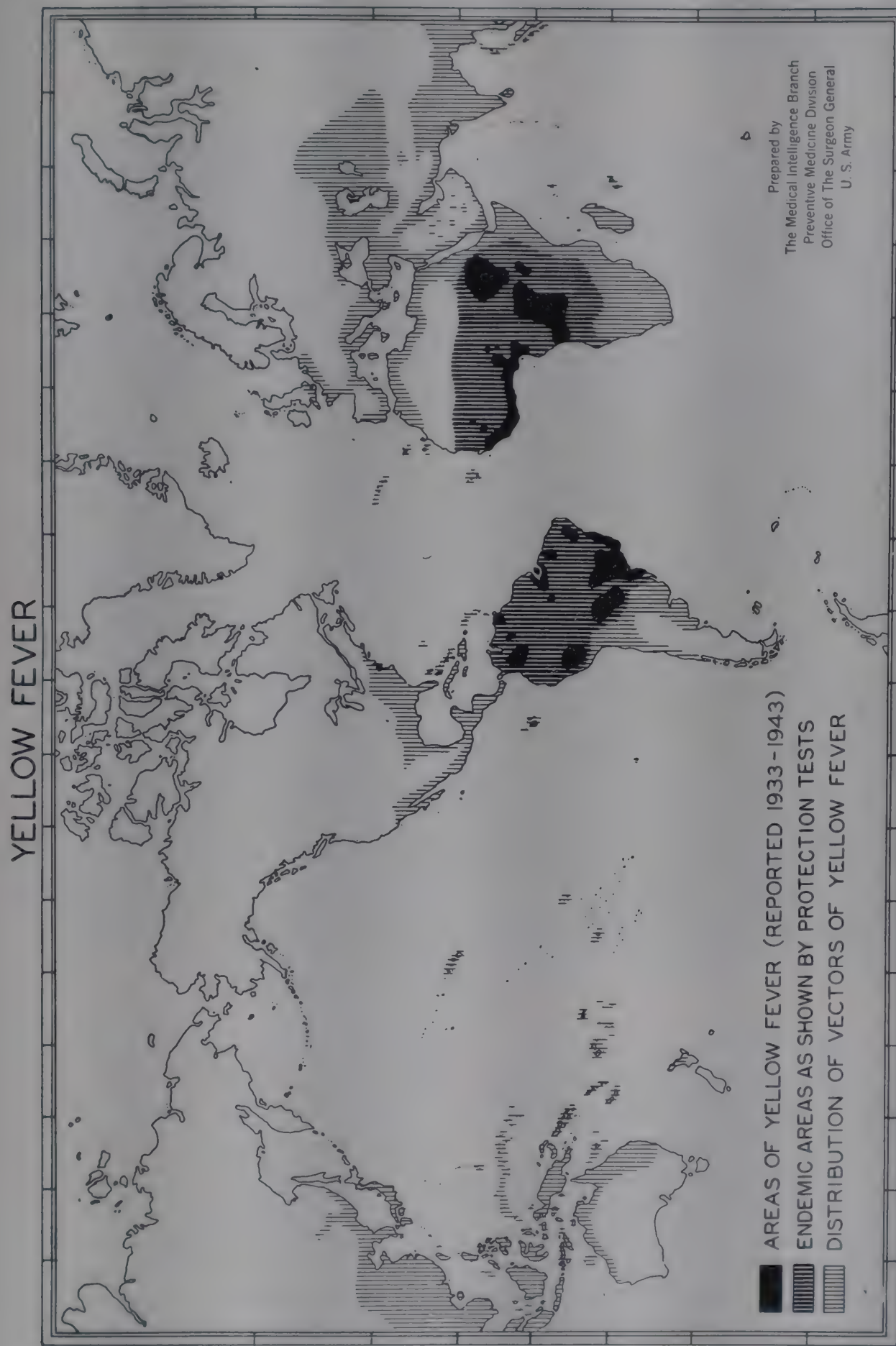


Fig. 200. Worldwide distribution of yellow fever.

Clinicopathologic Correlation. The onset of yellow fever is sudden and is characterized by the general signs of invasion and infection of the body, such as fever, headache, backache, tenderness of the muscles, nausea, and vomit-

renal tubular epithelium gives rise to albuminuria, hematuria, and, in fatal cases, uremia. The cause of the typical bradycardia is not clearly understood, but it is probably associated with the jaundice. A hypoprothrombin-

emia, dependent on damage to the liver, is probably the cause of the hemorrhage into the various tissues. The principal manifestation of hemorrhage is the black vomitus, caused by hemorrhage into the stomach. In fatal cases death usually occurs during the second week (Elliott).

Infectious Hepatitis and Serum Hepatitis

A disease of the liver, characterized by marked degeneration and necrosis of the hepatic cells, has been known for at least a

Knowledge of the pathologic changes in *nonfatal cases* is based on biopsy studies. Early there are all types of degenerative changes in the hepatic cells, which lose the orderly columnar pattern of lobules. In the central zone the change is usually more advanced with necrosis and loss of cells. The portal space is infiltrated with mononuclear cells and few leukocytes (Dible, McMichael, and Sherlock).

In the *fulminant* fatal cases with death in three to ten days after onset of symptoms the liver is reduced in size, soft, and a mottled yellow red color. The entire parenchyma is

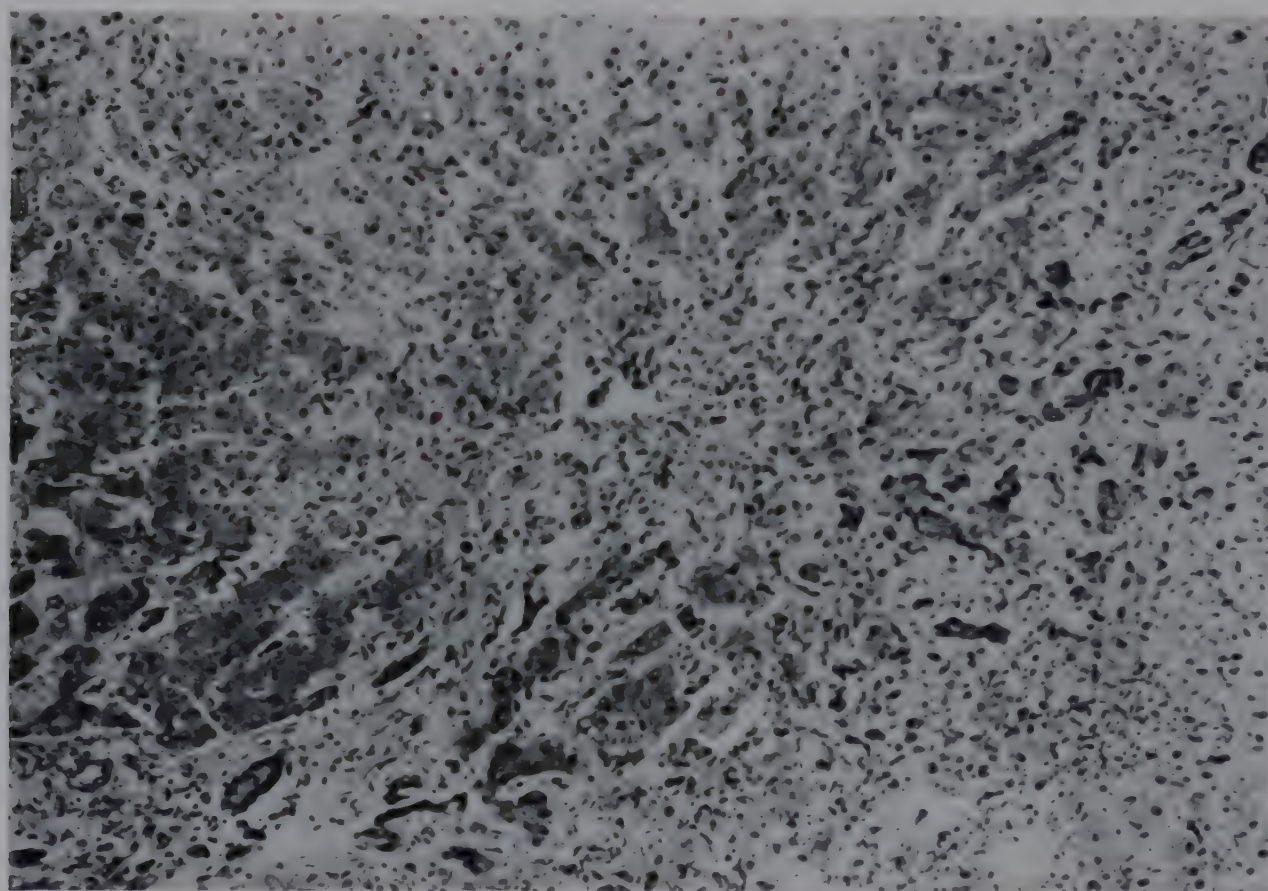


Fig. 201. Liver in infectious hepatitis.

century. It had been observed sporadically, endemically, and epidemically, but it was not until World War II that these various forms were recognized as a clinical entity.

On the basis of epidemiologic and viral studies between 1940 and 1945, it became apparent that there are two etiologic entities: infectious hepatitis which is acquired by the gastro-intestinal route, and serum hepatitis which is transmitted by plasma and blood transfusions. There is no cross-immunity, indicating the existence of two distinct viruses.

Pathologic Anatomy. Pathologic changes in infectious hepatitis and serum hepatitis are the same and may be considered under the titles: nonfatal cases, fulminant cases, acute fatal cases, and subacute cases.

destroyed and represented as a granular necrotic debris embedded in the collapsed supporting tissue. The portal spaces are infiltrated with mononuclear cells, plasma cells, and lymphocytes, with a few leukocytes and eosinophils (Lucké and Mallory).

In *fatal cases* with survival for longer periods there is a mixture of preserved liver cells, necrotic liver cells, and regenerated liver cells. The lymph nodes at the hepatic hilum are enlarged and edematous. The spleen is enlarged as the result of congestion and hyperplasia. The intestinal wall is frequently edematous and in a few patients there is phlegmonous inflammation, especially of the cecum. The brain shows degeneration of nerve cells and rarely a mild meningo-encephalitis

characterized by infiltration of lymphocytes. The bone marrow is hyperplastic. Hemorrhages are present in many tissues (Lucké).

In most instances recovery is complete and the liver is restored to anatomic normality (Lucké). However, in a few patients the disease becomes *subacute* or there are relapses.

fifty-six to 134 days. The jaundice results largely from destruction of liver cells, but blockage of the bile canaliculi may be a factor. The hemorrhage is of the hypoprothrombinemic type as a consequence of the destruction of liver. Human gamma globulin is useful in prevention (Havens and Paul).

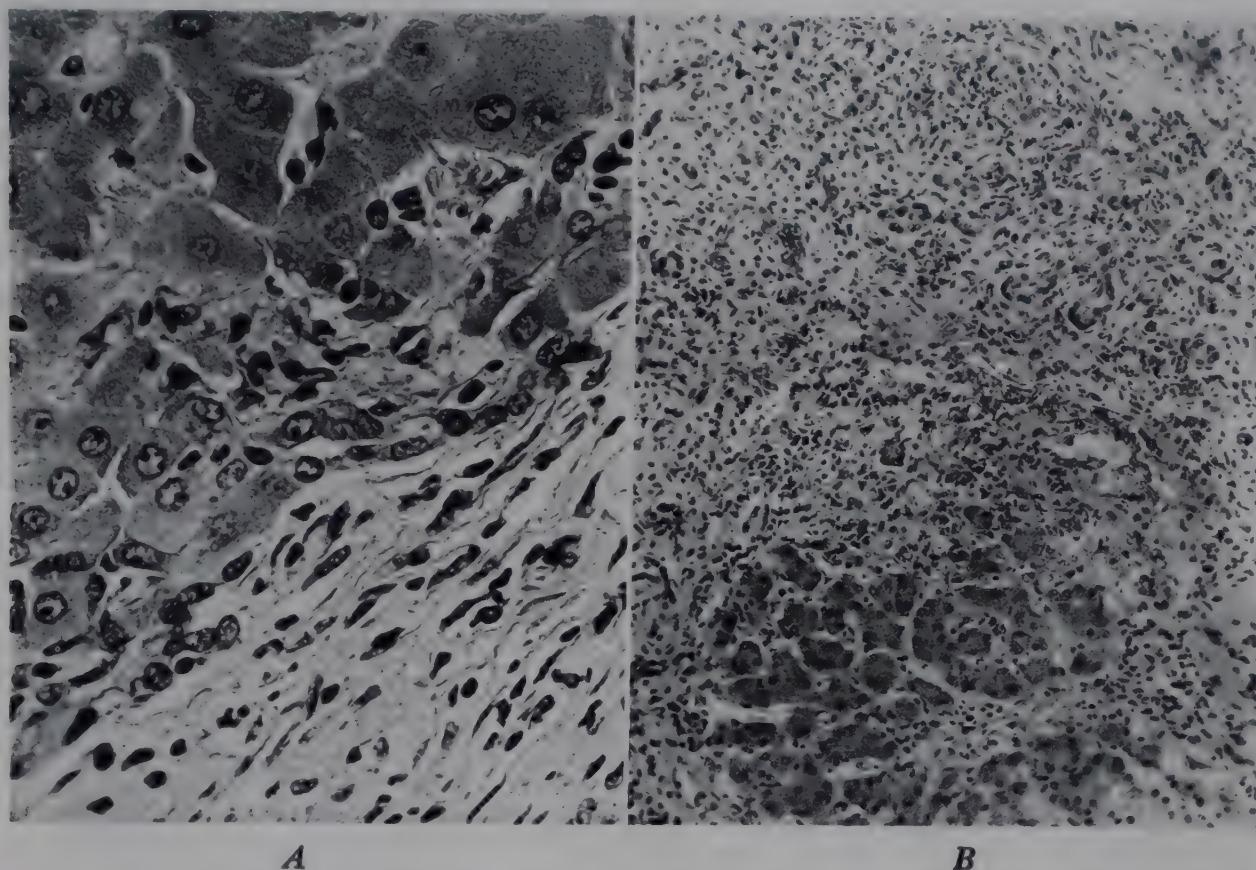


Fig. 202. Infectious hepatitis with regeneration. *A*, Junction of regenerating bile duct and hepatic cells. *B*, Destruction of parenchyma and cellular infiltration.

Under these conditions there is a definite cirrhosis of the lobular type (Dible, McMichael, and Sherlock).

Causal Agent. Information on the viral cause of the disease is based on administration of infectious material—serum and stool—to human volunteers. Both viruses pass through a filter, but the virus of serum hepatitis is not infectious by mouth and is not present in the stool. Virus may be readily recovered during the incubation period and early stages of the disease, but only rarely thereafter. Stokes has grown the virus in embryonated eggs.

Transmission. Infectious hepatitis is probably transmitted by direct contact and in epidemics through water and food. Serum hepatitis is transmitted by plasma and blood transfusions, by contaminated syringes, and by vaccines containing human serum.

Clinicopathologic Correlation. The incubation period of infectious hepatitis is fifteen to thirty-four days and of serum hepatitis is

Catarrhal Jaundice. This is the sporadic type of infectious hepatitis and there is no basis for the original concept of a mucous plug blocking the common bile duct.

Influenza

During 1918 and 1919 there was throughout the world a pandemic of an acute respiratory disease known as influenza. At first it was thought that this was a new disease, but careful study showed that there was a similar pandemic in 1889–1891. The disease is of interest not only because of the pathologic changes and clinical signs which it produces itself, but because of the manifold complications and secondary infections with bacteria which are common during a pandemic period.

Pathologic Anatomy. The pathologic changes are largely limited to the respiratory tract, specifically the trachea, bronchi, and lungs. The mucosa of the trachea and bronchi is dark red or purple, swollen, soft, and

velvety. Throughout the mucosa there are numerous small, superficial ulcerations, 1 to 2 mm. in diameter. The lungs are collapsed, dark purple, and leathery in the affected areas. In the unaffected areas they are pale and emphysematous. Beneath the pleura and in the peritruncal tissues there is interstitial emphysema. In some cases this extends into the mediastinum and into the subcutaneous tissues of the neck and thoracic wall, where it is clearly discernible on close examination. The architecture of the lung is obscured in the red and purple areas. The small bronchioles are filled with a yellow, thick fluid. The blood vessels are congested and a quantity of frothy, red fluid can be expressed from the cut surfaces. The pleural cavity usually contains an increased quantity of fluid, and the pleural surfaces are covered by a fine fibrinous exudate. The lymph nodes at the hilum of the lungs and throughout the body are enlarged and soft, and on section appear red and finely granular. The spleen is moderately enlarged and the splenic pulp is soft, with conspicuous malpighian bodies. The liver may be slightly enlarged and soft. There are occasional small petechiae and ecchymoses in the cortex of the adrenal glands. There are no essential pathologic changes in the other organs.

The bronchioles are filled with polymorphonuclear leukocytes, fluid, and fibrin. The walls of the bronchioles are edematous, congested, and infiltrated with leukocytes and lymphocytes. Most of the alveoli are collapsed. In the affected regions the alveolar walls are swollen and thickened by congestion and infiltration with cells. Within the alveoli there is a small amount of exudate composed of red blood cells, mononuclear cells, and a rare polymorphonuclear leukocyte. Within many of the alveoli there is a thin hyaline membrane which lines the space and is firmly adherent to the wall. In the lung immediately adjacent to the affected areas there are dilated alveoli and small foci of interstitial emphysema. The essential changes in the lymph nodes are edema, congestion, and hyperplasia of the endothelial cells of the sinusoids. There is cloudy swelling of the parenchymal cells of the liver and kidneys (Wolbach and Frothingham; Goodpasture; Winternitz, Wason, and McNamara; MacCallum; Opie, Freeman, Blake, Small, and Rivers.)

It is difficult to separate accurately the path-

ologic changes caused by the virus of influenza from those caused by secondary bacterial invasion. The changes described in the preceding paragraph are those generally seen in the absence of severe bacterial infection. The streptococcus, producing an interstitial bronchopneumonia, the pneumococcus, associated with a typical lobar pneumonia, the staphylococcus, bringing about a pneumonic process with formation of numerous small abscesses, and the influenza bacillus are the most common secondary bacterial invaders. It is difficult to evaluate any particular pathologic changes caused by the influenza bacillus. It is thought by some that the hemorrhagic lesions and the ulcerations are more likely to occur when this bacterium is present. It has also been suggested that the venous thrombi throughout the body are prone to occur with secondary invasion by the influenza bacillus.

Causal Agent. The virus of influenza is readily isolated by the intranasal inoculation of pharyngeal washing into ferrets (Smith, Andrewes, and Laidlaw). After acclimatization in this animal, the virus can be propagated in mice by intranasal inoculation under light ether anesthesia (Andrewes, Laidlaw, and Smith). Mice die on the fourth to the seventh days, and in the lungs the numerous small hemorrhagic foci are similar to those in man. Serum from a person who has had the disease, or from an animal which has recovered, contains neutralizing bodies which will protect the mouse against the virus. The virus can be grown on the chorio-allantoic membrane of the chick embryo (Francis and Magill). The serum of human beings and of animals exposed to the virus contains complement-binding bodies which react with an antigen prepared from the ground-up lung of an infected mouse (Lennette and Horsfall). With neutralization tests and with the complement fixation reaction, it has been shown that there are at least two strains of the influenza virus, designated A and B. Suspensions of influenza virus agglutinate chicken red blood cells in direct proportion to the lethal titre for mice and immune serum inhibits the reaction (Hirst).

Transmission and Epidemicity. Influenza is transmitted from person to person by the secretions of the nose and pharynx, specifically by coughing and sneezing. It is estimated

that 548,000 people died of influenza in the United States during the years 1918 and 1919 (Francis). Shortly after the epidemic of influenza, there was an epidemic of lethargic encephalitis. The relation of these two diseases is fully discussed in the section on the latter (p. 405).

Clinicopathologic Correlation. Invasion of the body by the virus of influenza brings about striking symptoms and signs of an infectious process: headache, nausea, vomiting, prostration, and pains in the muscles. The localizing signs of the infection in the respiratory tract

larly firm. The pleura is usually smooth and glistening, although there may be a few small petechiae in the subpleural tissues. The cut surface of the lung is dark purple in color, and the architecture is not visible. Throughout the substance of the lung, more particularly in the lower lobes, there are indefinite, discrete and confluent, spherical nodules, with a small amount of air-containing tissue between them. These nodules are slightly elevated, dark red, and firm. The mucosa of the trachea and bronchi is swollen and red. Many of the smaller bronchi are completely occluded by a

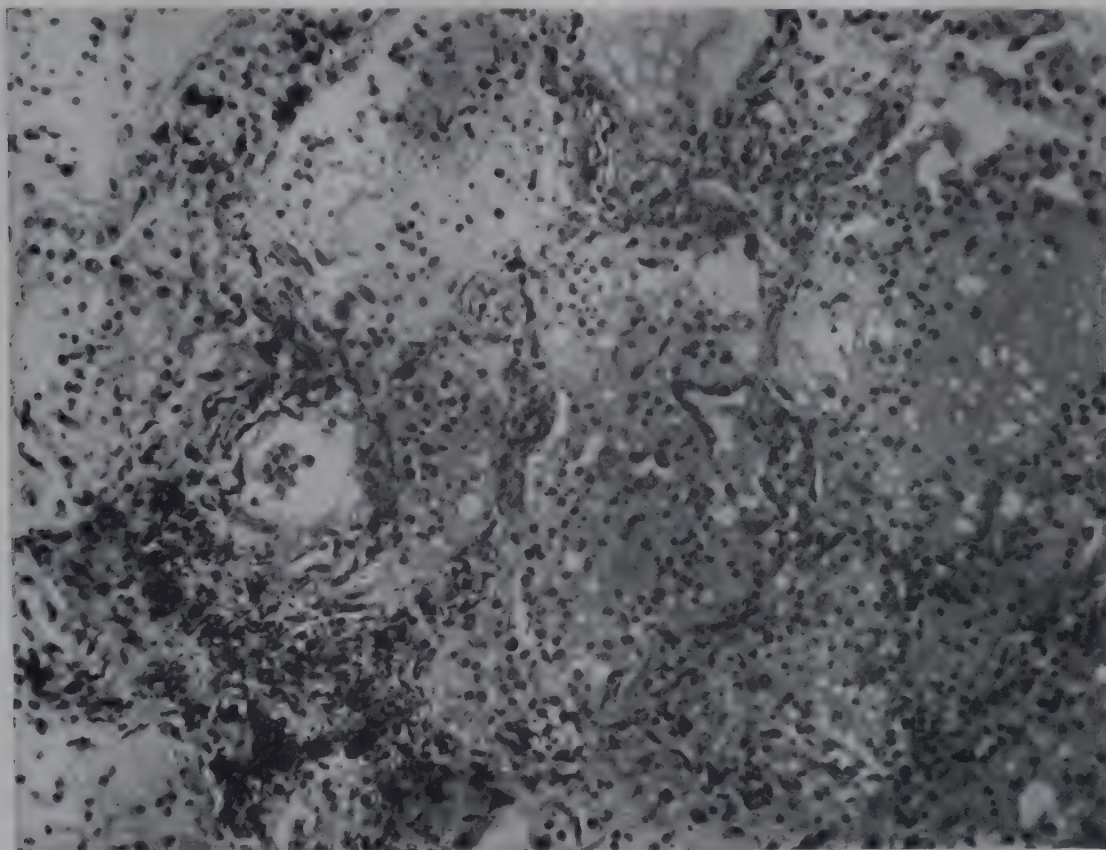


Fig. 202a. Pneumonia in psittacosis. (Tissue by courtesy of Dr. Ralph Lillie, U.S.P.H.S.)

are a sore throat, which looks dark red and velvety, and difficulty in respiration because of the filling of the bronchioles with a purulent exudate and the formation of hyaline collars in the alveoli. The dyspnea may be extreme. If secondary infection with the pathogenic cocci supervenes, there are many signs and symptoms, and grave complications and sequelae. The more important of these are empyema, otitis media, meningitis, and pyemia.

Psittacosis

Pathologic Anatomy. Psittacosis in man produces characteristic pathologic changes in the lungs, liver, and spleen. The lungs are voluminous, dark reddish purple, and irregu-

thick, viscid material. Throughout the liver and spleen, which are generally enlarged and soft, there are small yellow foci of necrosis, not exceeding 2 mm. in diameter. In microscopic sections the character of the pneumonia is in part dependent upon the stage of the disease. Up to the fourth or sixth day the alveoli are filled with large numbers of red blood cells and polymorphonuclear leukocytes, entangled in a rich network of fibrin. After the sixth day the red cells and leukocytes are replaced by large mononuclear cells. At the same time there is extensive desquamation of the alveolar epithelium, and in some instances hyperplasia of the alveolar epithelium, with many mitoses. The severity of the pneumonic process varies from field to field. In some there is only fluid, in others

there is an intense inflammatory reaction with necrosis and formation of abscesses. Many of the mononuclear cells are desquamated; epithelial cells show fine droplets of fat in the cytoplasm. The interstitial tissue is edematous, hyperemic and infiltrated with mononuclear cells. With Giemsa's stain, small coccoid or bacillary bodies, not over 0.2 micron in diameter, are occasionally found in the alveolar epithelial cells. Small blood vessels are not infrequently occluded by thrombi. The lymph nodes are large and show edema, hyperemia, and desquamation of endothelial cells. In the spleen and liver the small yellow foci are typical areas of focal necrosis, with infiltration of mononuclear cells. In the central nervous system there are edema, hyperemia, and small foci of hemorrhage, both in the meninges and in the substance of the brain (Lillie).

Causal Agent. The virus of psittacosis is pathogenic for monkeys, rabbits, guinea pigs, and mice. The best method of inoculation is intracerebral, but in monkeys and rabbits intratracheal or intranasal inoculation will produce the disease. The most useful experimental procedure is the intraperitoneal inoculation of mice with macerated liver and spleen from an infected animal or man. In monkeys, parrots, and rabbits one attack of the disease confers solid immunity. In mice little immunity develops after recovery (Rivers, Berry, and Sprunt). The small coccoid or bacillary bodies occasionally seen in man and observed regularly in parrots are apparently the infective agents (Bedson).

Transmission. Undoubtedly psittacosis in man is acquired from contact with parrots or with their excreta. The virus is present in the feces and nasal secretions of these animals (Rivers, Berry, and Sprunt). Although the virus is present in the sputum of ill human beings, there is only slight evidence that the disease is passed from man to man. There is considerable evidence that apparently healthy psittacine birds may harbor the virus and pass it on to other birds or to man (Berry and Rivers). It has been suggested that the only satisfactory criterion for the release of birds from quarantine on entry to a country is a negative complement-fixation reaction (Meyer and Eddie). The last major outbreak in the United States was in 1930, and public health measures since that time have satisfactorily controlled the disease.

Clinicopathologic Correlation. The signs and symptoms of psittacosis are essentially caused by the infection and by the pneumonia. The symptoms of the infection are outstanding and severe—occipital headache, high fever, pains in the muscles, and easy fatigability. The signs and symptoms of the pneumonia are those of a massive consolidation, with complete flatness to percussion and complete absence of breath sounds. The incubation period is from five to ten days, and weak neutralizing and complement-binding bodies appear in the blood stream in from one to two weeks.

Ornithosis. Identical or similar viruses have been isolated from pigeons, chickens, and other birds. These viruses are pathogenic for man and produce a clinical disease resembling atypical pneumonia (Smadel, Wall, and Gregg).

Mumps

Pathologic Anatomy. Although epidemic parotiditis has been known since the days of Hippocrates, there is little conclusive knowledge concerning the alterations in the parotid gland in man. A few reports in the literature, together with observations in monkeys, may be used to reconstruct the picture. The gland is enlarged and pink, with small petechiae throughout the parenchyma. The alterations may be focal or diffuse. The interlobular and intralobular connective tissue is edematous and is infiltrated with mononuclear cells and a few lymphocytes. This change is particularly prominent about the ducts. Individual epithelial cells of the acini and of the ducts are swollen, vacuolated, and necrotic (Johnson and Goodpasture). Within the epithelial cells, at least in monkeys, there are small, vacuolated, cytoplasmic inclusion bodies, 4 microns in diameter. These bodies cannot, however, be considered diagnostic of the disease since they may be produced in monkeys by the injection of any of a great variety of substances (Bloch).

Causal Agent. The virus of mumps can be demonstrated in monkeys by the injection into Stenson's duct of a filtrate of saliva from patients with epidemic parotiditis. The monkeys acquire a typical clinical disease, and pathologic studies of the parotid gland show lesions similar to those which have been de-

scribed in man. The initial injury is epithelial, with necrosis of individual cells. There is a secondary inflammation of the interstitial tissue. During the early stages, the infiltrating cell is the monocyte, while later the lymphocyte is preponderant. The epithelial injury is repaired by multiplication of viable epithelial cells without scarring. Inclusion bodies are found in most instances (Johnson and Goodpasture).

Transmission. The incubation period of mumps varies from eight to thirty-five days, with an average of eighteen days. The secre-

caused by mumps is only rarely followed by sterility (Twinnem). A rare complication is acute hemorrhagic necrosis of the pancreas, an extension of an acute interstitial pancreatitis present in many. Of 6523 cases of mumps in New York City in 1929, 252 came to the Willard Parker Hospital. On the basis of clinical signs and symptoms an orchitis developed in twenty-seven of them, a pancreatitis in thirteen, a meningitis in two, and a thyroiditis in one (Brahdy and Scheffer). In many cases of mumps without neurologic signs and symptoms, examination of the spinal fluid will

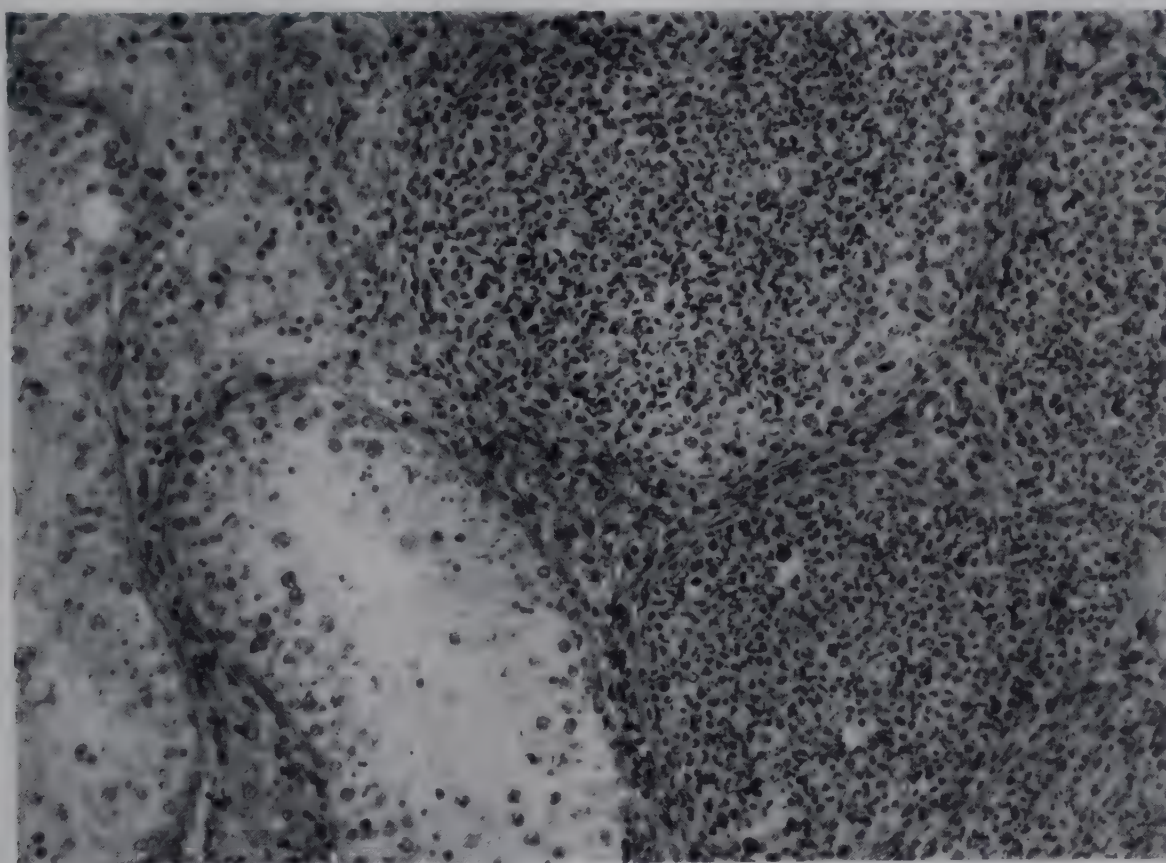


Fig. 203. Inflammation of testis in mumps. (Armed Forces Institute of Pathology, Neg. No. 70127.)

tions of the mouth contain the virus and it may be transmitted from man to man either directly or by fomites.

Complications. It has been customary to regard mumps as a disease of the parotid gland and to list involvement of any other tissue as a complication. It is probably more correct to assume that mumps is a systemic disease with localization in certain tissues, notably, the parotid, the gonads, the pancreas, and the meninges. The same general alteration is present in the testis as in the salivary gland: that is, necrosis of individual cells and a moderate to severe interstitial inflammation, with edema and infiltration of mononuclear cells. It is probable that if tissue is examined there is some degree of orchitis in every case of mumps. Despite the general impression, an orchitis

show a pleocytosis of lymphocytes up to 200 per cubic millimeter. In a rare case there is definite clinical evidence of a meningo-encephalitis (Brown, Kirkland, and Hein). Mumps encephalitis occurs without parotiditis (Kilham). From 3 to 5 per cent of deaf mutism has its basis in a neuritis of the eighth nerve during an attack of mumps (Boot).

Clinicopathologic Correlation. The symptoms of mumps are dependent on the local changes and the general infection. In the latter group there are malaise, headache, anorexia, and fever. In the former group there are a mild pharyngitis, swelling and tenderness over the affected salivary gland, usually the parotid, and swelling, tenderness, and pain about the orifice of Stenson's duct. The accumulation of secretion in the gland and in the duct

when there is inflammatory occlusion of the orifice is the basis of the pain often resulting from the eating of sour foods. There is a slight leukocytosis. In the uncomplicated case, the disease in the salivary gland lasts from four to eight days. In general, one attack confers lifetime immunity, but there are established examples of a second or even a third attack.

Colorado Tick Fever

Colorado tick fever, occurring in Colorado, Utah, Wyoming, Idaho, and Oregon, has been known for many years, but it was not until 1944 that the viral cause was established (Florio and Stewart).

Pathologic Anatomy. Nothing is known of the pathologic changes in man. In hamsters there is hyperplasia of the splenic follicles with intracytoplasmic basophilic and eosinophilic inclusions in the mononuclear cells in the follicles.

Causal Agent and Transmission. The virus is present in the blood and is infectious for hamsters, mice, cotton rats, opossum, and the yolk sac of chick embryos. The wood tick, *Dermacentor andersoni*, transmits the virus. Complement-fixing and neutralizing antibodies can be demonstrated.

Clinicopathologic Correlation. The disease consists of two to three sharply limited febrile periods with general symptoms lasting about forty-eight hours.

Dengue Fever

The word "dengue" is probably derived from the Spanish word "danguero" meaning dandy. It was applied because of the stiff gait of persons afflicted with the disease. Dengue is also known as "break-bone fever." It is characterized clinically by febrile paroxysms, pains in the joints and muscles, leukopenia, and variable initial and terminal rashes. Recovery is the rule in from seven to ten days, but apathy and mental depression may continue for some time.

Pathologic Anatomy. Because of the low mortality there are no adequate pathologic studies. It is said that there are cloudy swelling and fatty degeneration of the viscera and petechiae of the gastro-intestinal tract.

Transmission. The virus is present in the blood stream during the early days of the

disease, and monkeys (*Macaca philippinensis*) are susceptible to artificial inoculation, and also probably have the disease naturally. The virus is biologically transmitted from man to man, from monkey to monkey, and possibly from monkey to man by the *Aedes aegypti* mosquito. There is immunity following the disease, but second and even third attacks have been recorded.

Phlebotomus Fever

Phlebotomus, pappataci, or sandfly fever is a disease occurring in areas harboring the sandfly, *Phlebotomus papatasi*; these areas are mainly between 20 and 45° north latitude in Europe, Africa, and Asia (Sabin).

Pathologic Anatomy. Nothing is known of the lesions in man because of the negligible mortality in the uncomplicated disease.

Causal Agent. The virus is between 40 and 160 millimicrons in diameter and may be grown on the chorio-allantoic membrane of the chick embryo. It is not infectious for any experimental animal and all studies have been on human volunteers.

Clinicopathologic Correlation. The incubation period is two to six days. Aside from conjunctivitis and enlargement of lymph nodes, the signs and symptoms are largely those of an acute infection—headache, malaise, pain in muscles and joints, and fever. The relation of the leukopenia to the bone marrow and lymph nodes is not known.

Viral Diarrhea and Stomatitis

A disease of infants, frequently in the form of "epidemic diarrhea of the newborn," and rarely of adults is caused by a virus (Buddingh).

Pathologic Anatomy. The intestinal contents are watery, greenish yellow in color, and contain large amounts of mucus. The mucosa is swollen and contains petechiae, some of which show ulceration. The microscopic features are edema, congestion, focal necrosis of the mucosal epithelium, and infiltration with leukocytes. The mesenteric nodes are enlarged and edematous. Lesions similar to those in the intestine may be present in the buccal cavity.

Causal Agent. The virus can be demonstrated by inoculation of stool or scrapings

from the buccal cavity onto the scarified cornea of the rabbit's eye. The reaction is a cloudy opacity along the scarified lines, palpebral congestion, and sometimes iritis. Neutralizing antibodies are present in man and rabbits after exposure to the virus. Diarrhea can be produced in young rabbits.

Clinicopathologic Correlation. The primary symptom, diarrhea, is related to the inflammation of the intestine. The disease in adults, apparently acquired by direct contact with sick infants, is limited to a stomatitis.

Miscellaneous Viscerotropic Viral Diseases

Pretibial Fever. Also known as Fort Bragg fever, this condition, characterized by prostration, fever, splenomegaly, a rash on the legs, respiratory infection, and leukopenia, was first observed in 1942 (Daniels and Greennan).

A filterable agent pathogenic for guinea pigs, rabbits, embryonated eggs, and hamsters, lethal for the latter, has been recovered. Neutralizing bodies are present in the serum of convalescents and the human disease has been reproduced in volunteers by parenteral injection of active material (Tatlock).

Rift Valley Fever. This is a disease of sheep and cattle in Kenya Colony, Africa. Laboratory infections have been reported and it is possible that what is called three-day fever in Africa is in part Rift Valley fever in man (Sabin and Blumberg).

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Diseases Caused by Viruses: Neurotropic Viral Diseases

The viruses which cause inflammation of the tissues of the central nervous system have little in common except organ specificity. The viruses vary greatly in size, are immunologically distinct, produce varying types of pathologic change, and are transmitted to man in different ways.

A list of the viral encephalitides includes poliomyelitis, Western and Eastern equine encephalomyelitis, Venezuelan equine encephalomyelitis, St. Louis encephalitis, Japanese B encephalitis, Russian tick-borne (Far Eastern) encephalitis, lymphocytic choriomeningitis, pseudolymphocytic choriomeningitis, swineherd's disease, louping ill, and rabies. Not included in this chapter because their viral nature is not established are lethargic encephalitis (Chapter LI) and acute disseminated encephalomyelitis (Chapter CVII). It should be remembered that other viral diseases, primary in the skin or viscera, may at times involve the brain, notably herpes simplex, mumps, and measles.

Poliomyelitis

Poliomyelitis, or infantile paralysis, has been recognized as a distinct entity since the original descriptions by Heine in 1840 and by Medin in 1890. Despite the fact that Wickman in 1905 described both paralytic and nonparalytic or abortive types of the disease, the medical profession and the laity have continued to think of infantile paralysis as exclusively a disease of the central nervous system, an idea that is false and misleading.

Pathologic Anatomy. The pathologic changes as seen at autopsy are not confined to the central nervous system. There are distinct lesions in the lymph nodes, spleen, liver, and other viscera. The brain and spinal cord are congested and may be of decreased con-

sistency. The pial blood vessels are conspicuous, and on section numerous small bleeding points and petechiae are seen, especially in the brain stem and spinal cord. The congestion and softening are more pronounced in the ventral gray horns of the spinal cord. Edema of the brain is reflected in a bulging of the



Fig. 204. The spinal cord in poliomyelitis. Note the swelling of the entire cord and the congestion and hemorrhage in the ventral gray horns.

cut surface from beneath the meninges. The liver and kidneys are slightly enlarged and soft and the parenchyma may bulge from beneath the capsule. The spleen is slightly enlarged and the malpighian bodies are unusually conspicuous. The lungs are edematous and congested; and in the patients with bulbar paralysis, pneumonia from aspiration is a

common occurrence. The lymph nodes throughout the body are enlarged and soft, and the cut surface is pink or red and finely granular.

There is a slight infiltration of the subarachnoid space with lymphocytes, monocytes, and polymorphonuclear leukocytes, most severe in the ventral fissure of the spinal cord, and inconspicuous or absent over the cerebral hemispheres. Throughout all parts of the spinal cord and brain stem there is cellular infiltration with lymphocytes and occasional leukocytes, most pronounced in the perivas-

are congestion, slight interstitial edema, cloudy swelling, and occasionally infiltration with lymphocytes. In the liver there are small foci of necrosis (Flexner, Peabody, and Draper). In the lymph nodes and in the spleen there are hyperplasia of the primary follicles, proliferation of the lining endothelium of the sinusoids, congestion, and edema (Burrows).

In persons who recover from an acute attack and die months or years later from another cause, the involved segment of the spinal cord is smaller than normal and there

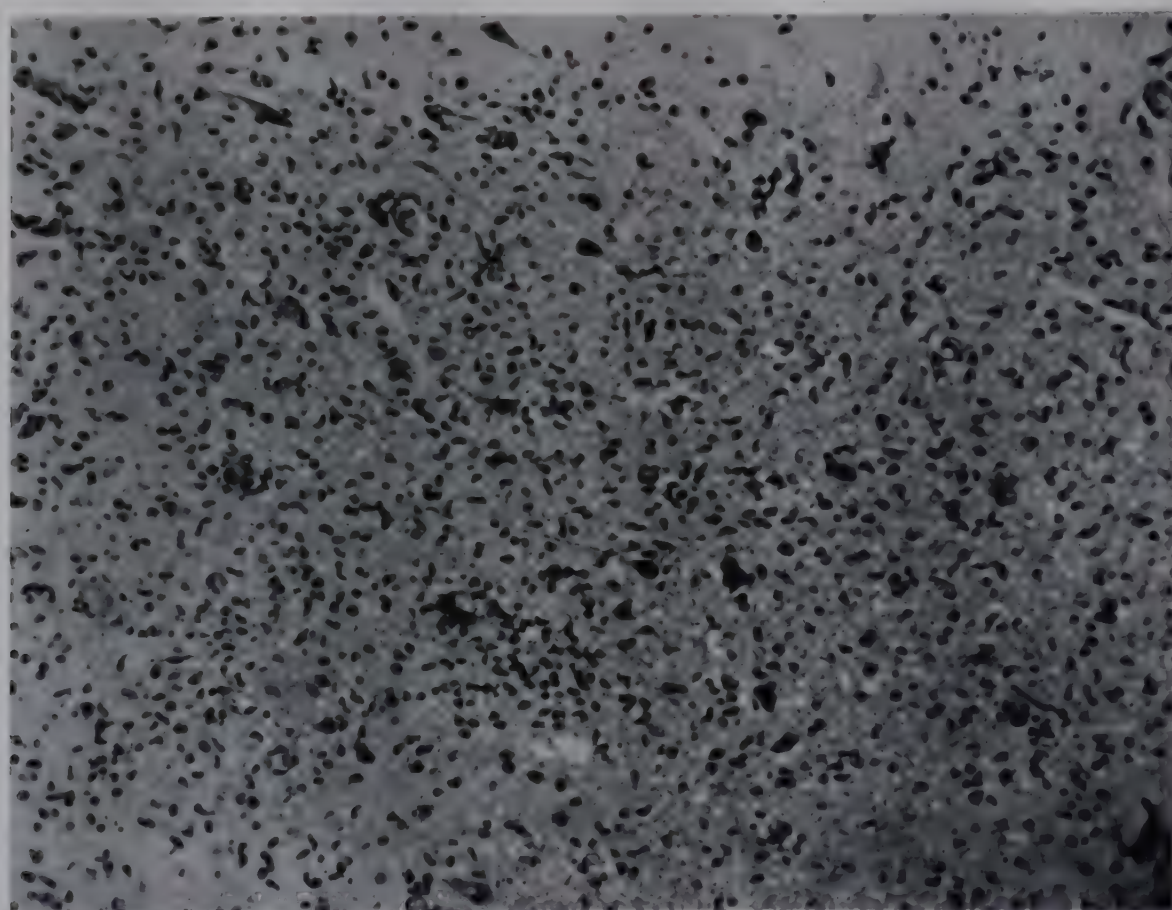


Fig. 205. Ventral horn of spinal cord in poliomyelitis. There is an infiltration of lymphocytes and leukocytes, and the ganglion cells have undergone necrosis.

cular lymphatic spaces. In the ventral gray horns of the spinal cord and in the bulbar nuclei there are an intense inflammatory reaction with necrosis of tissue, infiltration with cells, and chromatolysis and necrosis of the ganglion cells. Similar but less severe changes are occasionally found in the mesencephalon, but lesions in the cerebral cortex and in the cerebellum are rare. Lesions in the medulla are most common in the reticular substance, nucleus ambiguus, and supraspinal and spinal accessory nuclei (Peers and Lillie). The peripheral nerves derived from the involved ganglion cells show degeneration of the axis cylinders and breaking up of the myelin sheaths (Abramson; Howe).

Throughout all of the solid viscera there

is a decrease or absence of ganglion cells. The ventral horn is represented by a mass of interwoven, fibrillary astrocytes. The affected nerves are completely degenerated, and the paralyzed muscles are the seat of a typical neurotropic atrophy.

Causal Agent. The virus of poliomyelitis is readily recovered from human material by the intracerebral and intranasal inoculation of monkeys (Sabin and Ward). The pathologic lesions in the monkey are similar to those in man (Hurst). In the blood of many normal persons, and of both animals and man after recovery from the disease, there are neutralizing bodies which when injected with the virus protect against infection. Largely because of the lack of understanding of the mechanism

of the action of the neutralizing bodies, they cannot be used for quantitative studies, but only for qualitative surveys of large numbers of sera (Schaeffer and Muckenfuss). Studies are not yet complete, but there are apparently three basic immunologic types of the virus (Bodian, Morgan, and Howe). Failures in vaccination may be related to diversity of types.

Transmission. In the early experimental studies of poliomyelitis it was concluded that the virus entered the body through the nose and invaded the central nervous system by way of the olfactory bulbs (Flexner and Amoss; Brodie and Elvidge). The demonstration that the olfactory bulbs do not show pathologic change in most human cases of poliomyelitis (Landon and Smith) challenged this conclusion; as did the observation that lesions of the olfactory bulb in monkeys are present only after intranasal instillation and do not occur after other types of inoculation (Sabin and Olitsky). It was suggested that any of the peripheral or visceral nerves, of which the olfactory nerve is only one, might serve as the portal of entry (Bodian and Howe). In the last twelve years a great mass of evidence has accumulated to overthrow completely and finally the theory that the nose is the portal of entry. The more important of these observations are: human poliomyelitis may follow subcutaneous inoculation of the virus and the segment of the spinal cord first affected depends on the site of inoculation in the skin (Leake); the virus is present in the stools in relatively high concentration; suspensions of stool are a stable medium for the preservation of the virus; in abortive cases, the virus is easily isolated from the stool (Trask, Vignec, and Paul); and the virus has been isolated from flies (Paul, Trask, Bishop, Melnick, and Casey). Sabin and Ward, who investigated the distribution of the virus in the various organs in human poliomyelitis, were able to recover the virus most frequently from the wall and contents of the intestine and from the medulla and spinal cord. It was rarely present in the olfactory bulbs. The mass of evidence today is that the virus is present in the pharynx and intestine. It is certainly spread through fecal contamination, and probably also by droplets from the mouth (Ward and Walters). The nervous system is invaded through the sympathetic and parasympathetic

nerves to the intestinal tract, either spinal or bulbar (Paul and Trask). In an occasional case, the virus enters through the wound of a tonsillectomy (Francis, Krill, Toomey and Mack).

Clinicopathologic Correlation. The incubation period of poliomyelitis varies from six to twenty days, and there is some evidence that infectiousness extends from the fourteenth day preceding the onset of symptoms to at least the fifth day of the disease (Aycock and Luther). The incidence of poliomyelitis varies according to the age and concentration. The decrease of cases with increasing age is a reflection of the immunity acquired by subclinical infection or by an abortive attack of the disease. The incidence also depends upon the season of the year, being highest in the summer and fall. Trauma and strain appear to be predisposing factors (Editorial, J.A.M.A.). The observation that thiamine deficient mice show less paralysis confirms the old clinical observation that the well nourished child is more susceptible (Foster, Jones, Henle, and Dorfman). It has been shown that only one person out of each hundred susceptible acquires the clinically recognizable paralytic poliomyelitis. The low incidence of the disease in the first few months or year of life may be accounted for by the placental transmission of antibodies (Aycock and Kramer).

The invasion of the body by an infectious agent results in the fever, headache, and gastro-intestinal disturbances that mark the onset of the disease. The early invasion of the nervous system is reflected in the usual symptoms of irritability of the nervous system: hyperesthesia and pain on passive motion. With beginning loss of function of individual ganglion cells, there is weakness, and finally paralysis. The most severe changes may be in any part of the cord or in the medulla. If in the medulla, there is destruction of the motor nuclei of the tenth, eleventh, and twelfth cranial nerves, causing difficulty in deglutition and respiration. The symptoms of involvement of the cerebral cortex with spastic paralysis are uncommon. Since the meningeal inflammation is slight, the usual clinical signs referable to the meninges are inconspicuous. Involvement of the dentate nucleus of the cerebellum gives rise to ataxia.

Circulatory collapse and sudden death is

related to a mild interstitial myocarditis (Saphir and Wile).

Some 30 to 100 per cent of all persons, depending on geographic location, have neutralizing bodies in their sera with no history of the clinical disease. Ninety per cent of adults of an urban population have positive sera (Aycock and Kramer). Despite the pres-

hours. Others may complain of mild upsets referable to the upper respiratory or gastrointestinal tract. As compared to families in which there is no case of poliomyelitis, these minor illnesses are significant (Paul, Salinger, and Trask). It is likely that these illnesses are nonparalytic poliomyelitis. In these families, the virus may be recovered from a high per-



Fig. 206. A stela of the XVIIIth Dynasty (1587–1328 B.C.) in the Carlsberg Glyptothek at Copenhagen, showing in the talipes equinus of the male figure evidences of infantile paralysis. (After Hamburger.)

ence of neutralizing bodies in the serum of convalescent patients, this serum has proved of no value in treatment (Park).

Abortive Cases. If, during an epidemic of poliomyelitis, other members of a family in which there is a clinical case of the disease are followed carefully, it is observed that a certain number will suffer from some minor illness. Some will have an acute febrile disease characterized by sore throat, headache, and vomiting, lasting for twenty-four to thirty-six

centage of the members (Wenner and Tanner). In monkeys, there are definite changes in the nervous system in the nonparalytic cases (Bodian and Howe).

Coxsackie Virus. From the stool of a number of patients suffering from a poliomyelitis-like disease, a distinct virus has been isolated alone or in association with that of poliomyelitis. Suckling mice are susceptible. There are inflammation and necrosis of the skeletal muscles, but no lesions in the central nervous

system (Dalldorf, Sickles, Plager, and Gifford). In so far as can be determined residual paralysis is minimal and recovery is the rule.

Rabies

Rabies and the rabid animal have been a source of fear to the human being since the earliest days of written history. Today rabies is present in most of the countries of the world and annually takes a toll of about one hundred lives in the United States. That rabies can be

the ependyma, particularly in the floor of the fourth ventricle, the inflammatory process takes on a nodular character. There are small foci, from 200 to 500 microns in diameter, in which the ganglion cells are completely necrotic, and the tissue in a roughly spherical focus is heavily infiltrated with lymphocytes and microglial cells. Throughout all of the affected parts of the brain there is moderate proliferation of the oligodendroglia and of the microglia. The degree of change in the spinal cord depends partly on the location of the

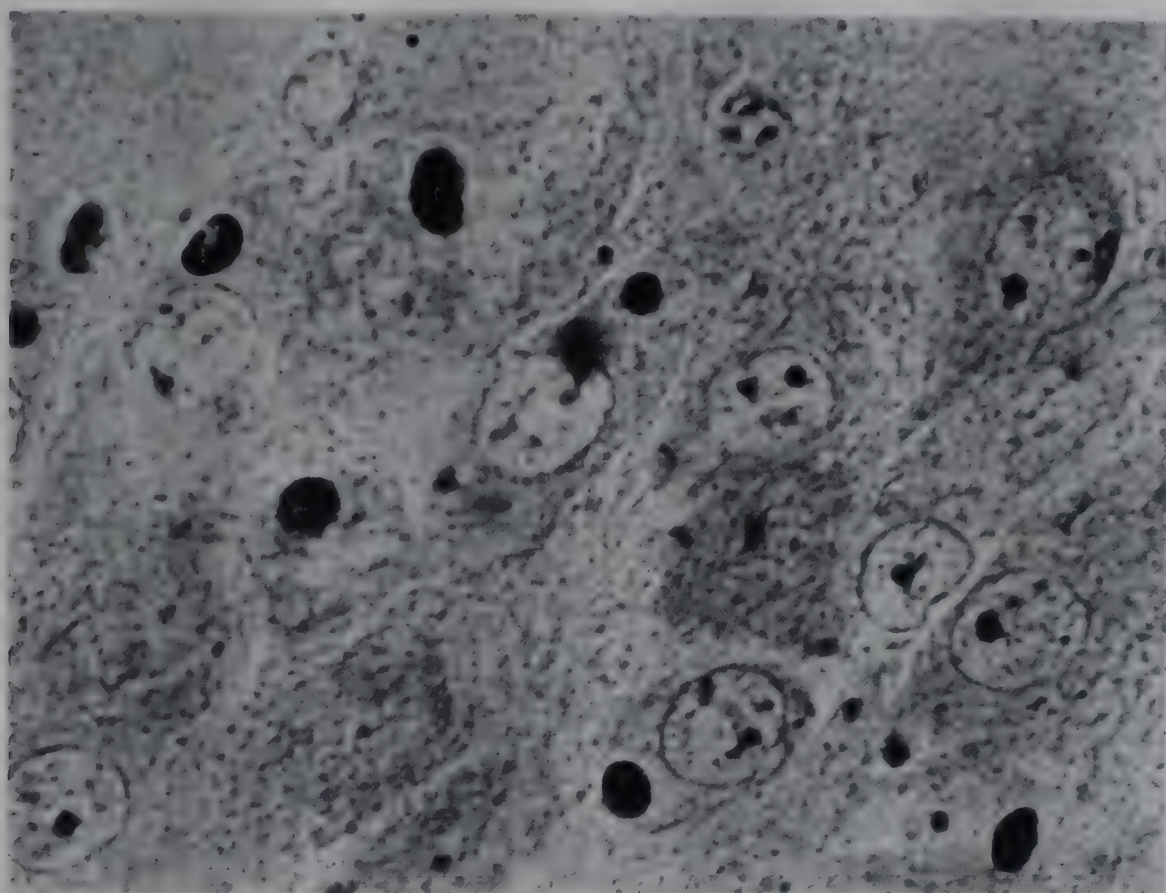


Fig. 207. Negri bodies in nerve cells. (Armed Forces Institute of Pathology, Neg. No. 74205.)

eradicated as a disease of both man and dogs is well shown by the work done in England, Sweden, and Australia (Rice and Beatty). It is estimated that approximately 16 per cent of all persons bitten by a rabid animal, if untreated, acquire rabies.

Pathologic Anatomy. The gross pathologic changes in the viscera and in the central nervous system are inconspicuous. There may be slight edema and congestion, and rarely visible areas of hemorrhage and softening. There are microscopic changes in the brain, in the spinal cord, and in all of the ganglia—cranial, spinal, and sympathetic. In the brain and cord there are edema, congestion, hemorrhage, and perivascular lymphocytic infiltration, affecting all parts, but more severe in the medulla and pons. Ganglion cells are necrotic, with prominent neuronophagia. Just beneath

bite. In persons bitten on the foot, the changes in the lumbar segment of the spinal cord are severe, while in persons bitten on the arm or face, the lower part of the spinal cord will show only minimal changes (Krinitzky). In the ganglion cells least affected, but especially in the hippocampus and in the cerebellum, there are the typical intracytoplasmic inclusion bodies known as Negri bodies (Horgan and McKinnon). The Negri body probably represents a degenerative change in the cytoplasm and the neurofibrillae (Goodpasture). In the ganglia there are necrosis of the ganglion cells, infiltration with lymphocytes, and a proliferation of the cells about each ganglion cell (Chachina).

Causal Agent. On December 6, 1883, at the International Congress in Copenhagen, and on February 24, 1884, at the French

Academy of Sciences, Louis Pasteur laid before the medical world his observations on a method for vaccination against rabies. Pasteur had found that the brain from a dog which had died of rabies would produce the disease when injected intracerebrally into rabbits. On the first transfer, the rabbit would die in from fourteen to twenty-one days. But on successive passage through the rabbit, the virus gained virulence and would kill in from four to seven days. With the increase in virulence for the rabbit there was a corresponding de-



Fig. 208. Louis Pasteur (1822–1895).

crease for the dog and for man. With further attenuation by drying, Pasteur developed the method universally used for antirabic vaccination, and first tried it on a young boy named Joseph Meister. The virus of rabies is pathogenic for practically every mammal, and of the laboratory animals the rabbit and certain susceptible strains of mice are the most satisfactory. In the latter animal, intracerebral or intraperitoneal inoculation brings about death in from four to six days, and neutralization tests are possible (Webster and Dawson).

Transmission. In modern times most cases of rabies in man are acquired from the bite of a rabid dog, but there are isolated cases in which the bite of a cat or other animal has

produced the disease. In a few unusual instances typical rabies, especially of the paralytic type, is not preceded by the bite of an animal (Knutti). The usual method for the diagnosis of rabies in an animal is the identification of Negri bodies in the ganglion cells of the hippocampus. As contrasted with the injection of susceptible mice, this morphologic diagnosis of rabies fails in 12 per cent of infected dogs (Leach).

Clinicopathologic Correlation. The incubation period of rabies varies from fourteen days to over a year. The invasion of the virus along the nerve trunks, and the degenerative changes in the corresponding spinal ganglia and spinal segments, give rise to the early symptoms of tingling in the bitten extremity and paralysis of that member. The severe degenerative and inflammatory changes in the medulla and pons result in the pharyngeal spasm and difficult respiration. The universal involvement of the brain, with degeneration of the ganglion cells, causes the late changes: coma and widespread paralysis. Damage to the hypothalamic centers probably brings about the glycosuria and other disturbances in vegetative function (Slotwer). It is generally assumed that the mortality from untreated rabies in man is 100 per cent.

Paralytic Rabies. In a certain number of cases of rabies the clinical signs and symptoms are those of an ascending paralysis of the Landry type. The usual clinical signs and symptoms are not present, and in at least some there is no history of a bite by a rabid animal (Knutti).

St. Louis Encephalitis

From July until October, 1933, there was in St. Louis and in St. Louis County, Missouri, an epidemic form of encephalitis with a morbidity rate of 100 per 100,000 population. A similar disease had been observed in Paris, Illinois, during August of the preceding year, in which the morbidity rate was 433 per 100,000. Concurrently with the epidemic in St. Louis there was a similar but less severe epidemic in other nearby cities (Leake, Musson, and Chope).

Pathologic Anatomy. The essential pathologic process is an acute, nonsuppurative inflammation of the central nervous system, characterized by severe vascular congestion with occasional petechiae, cellular infiltration

of the nervous system and meninges with lymphocytes and mononuclear cells, and degenerative changes in the ganglion cells. The brain shows congestion of the meningeal and intracerebral blood vessels, and there are small petechiae throughout the leptomeninges and in the substance of the brain. The gray matter is pink. Microscopically congestion and small perivascular hemorrhages are seen. About the blood vessels in the spaces of Virchow-Robin there is an infiltration of lymphocytes, large mononuclear cells, and plasma cells. In the severe cases the cellular

Causal Agent. The intracerebral injection of ground-up brain into monkeys (Muckenfuss, Armstrong, and McCordock) and certain strains of mice (Webster and Fite) produces a disease similar to that in man. The pathologic changes in the brain are identical with those described in the preceding paragraph. The serum from a human being or an animal that has recovered from the disease contains neutralizing bodies which protect against the virus in experimental animals. The virus is nonpathogenic for rabbits, rats, and guinea pigs, although it will survive in them

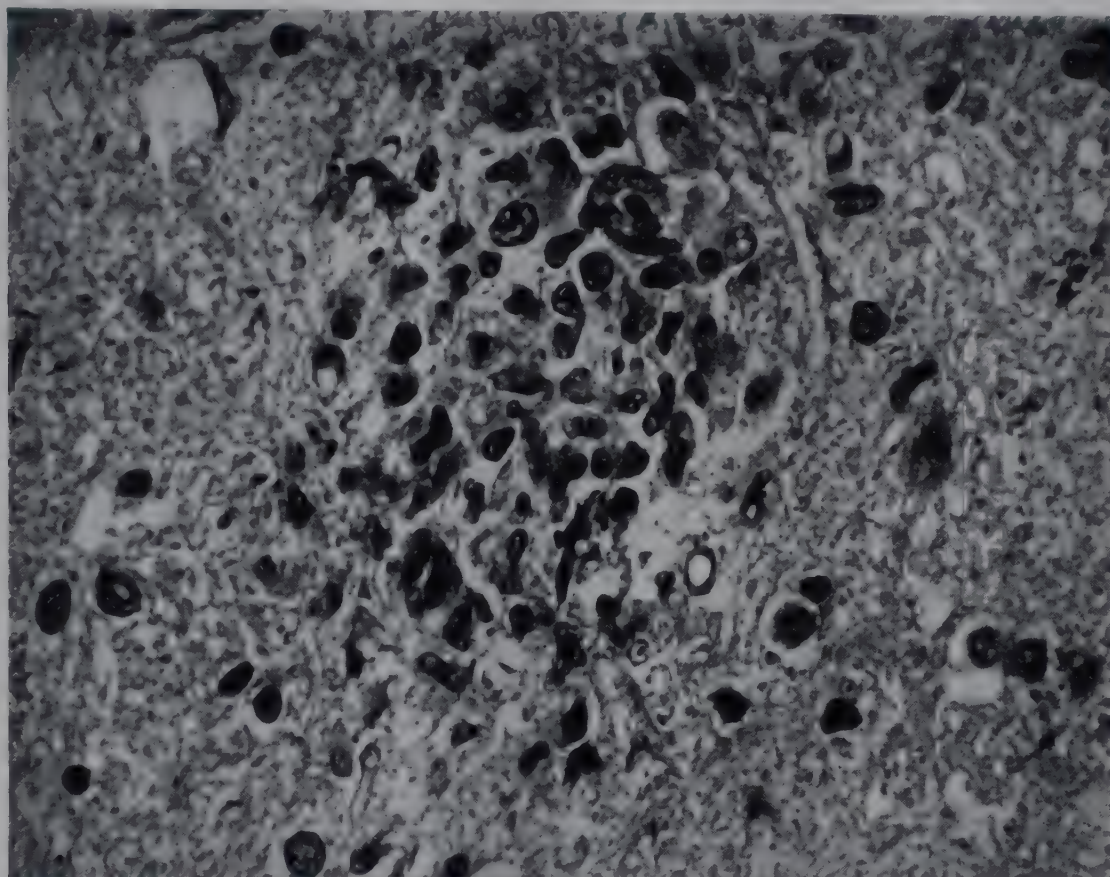


Fig. 209. Glial nodule in the brain in St. Louis encephalitis.

infiltration extends diffusely into the cerebral substance, with occasional small foci of necrosis. In the severely damaged foci there are a proliferation of microglia and the appearance of foam cells. Many of the ganglion cells show early necrosis, and neuronophagia is readily observed. The lesions are present in all parts of the brain and to a limited extent in the spinal cord. The most severe damage to nerve cells is in the pons, medulla, and basal ganglia. The nuclei of the cranial nerves are rarely affected. In the abdominal and thoracic viscera there are no characteristic changes; but cloudy swelling, congestion, and hemorrhage are frequently present in the kidney. There are no intranuclear inclusions in the central nervous system (McCordock, Collier, and Gray).

for a few days (Smith). The hamster is susceptible (Broun, Muether, Mezera, and Le Gier).

Transmission. The disease was far more common in St. Louis County than it was in the city, which fact led many to believe that transmission might be associated with water supply, milk supply, food, sewage, or some insect vector. The disease was more prevalent in areas close to weeds, refuse dumps, open sewers, or ponds (Casey and Broun). Smith, Blattner, Heys, and Miller have isolated the virus from chicken mites and shown that the virus is transmitted transovarially in the mite. The chicken develops a transitory viremia after inoculation or bite of an infected mite. In California the virus has been isolated from mosquitoes (Hammon and Reeves). It would

appear that the chicken mite is the reservoir and that the mosquito transmits the virus from the chicken to man.

Clinicopathologic Correlation. The incubation period of St. Louis encephalitis is difficult to determine, but it would appear to average between nine and fourteen days. The general symptoms of infection are extreme lassitude, malaise, chills, grippelike pains in the back or limbs, nausea or vomiting, and abdominal pains. Occasionally, there is an associated infection of the upper respiratory tract, and rarely photophobia. The specific signs of involvement of the central nervous system are a severe headache, stiff neck, mental confusion, and tremors. In some patients, the general symptoms predominate, while in others those resulting from involvement of the nervous system are more striking. In keeping with the slight infiltration of the meninges, there is a pleocytosis of some 50 to 250 cells with only slight changes in the sugar and globulin content of the spinal fluid (Hempelmann).

Japanese Type B Encephalitis. An encephalitis of Japan and China with similar anatomic changes is caused by a related but not identical virus (Smith). Mosquitoes are probably the vectors (Hammon, Reese, Casals, and Meiklejohn). The same virus causes an encephalitis of horses (Burns, Tigertt, and Matumoto).

Russian (Far Eastern) Encephalitis. A type of viral encephalitis observed in May and June and transmitted by the wood tick is seen in the Far East provinces of Russia and rarely in European Russia. The pathologic change is a severe inflammation with neuronophagia. The mortality rate is 30 per cent. Permanent neurologic sequelae are present in 20 per cent of those who recover. The virus is immunologically related to that of louping ill.

Australian X Disease. This disease was first observed in 1917-18 in Australia. A virus was isolated but was subsequently lost. Insofar as can be judged at present Australian X disease is similar to if not identical with Japanese B encephalitis.

Equine Encephalomyelitis

For many years a subacute encephalomyelitis of horses has been known in Europe under the term "Borna disease." In the sum-

mer of 1930 an acute encephalomyelitis of horses was observed in California, with a few instances of a similar disease in man. The virus isolated is known as the "western strain of equine encephalomyelitis." In the late summer of 1938 a similar epidemic appeared in Massachusetts. As in California, there were cases of the disease in man, especially children. The virus isolated from both the horses and from man is known as the "eastern strain of encephalomyelitis." The importance of this disease in horses is shown by the fact that in 1938 at least 184,000 cases were reported by veterinarians, with a mortality in the western variety of 25 per cent and in the eastern variety of more than 95 per cent.

Pathologic Anatomy. The meninges are intensely congested and the subarachnoid space is filled with a slightly turbid fluid. The brain substance is pink and unusually soft. All the changes are more conspicuous at the base than in the cerebral hemispheres. The spinal cord is moderately edematous and congested. Microscopically all parts of the brain, but especially the basal ganglion, the pons, and the medulla, are seen to be the seat of an intense inflammatory reaction. The subarachnoid space, the spaces of Virchow-Robin, and the brain substance are infiltrated with large numbers of polymorphonuclear leukocytes and small numbers of mononuclear cells, plasma cells, and lymphocytes. The blood vessels are dilated, and a few capillaries are filled with hyaline thrombi. In discrete and confluent foci there are necrosis of the brain substance and advanced infiltration with polymorphonuclear leukocytes (Fig. 217). There is no demyelination except in the areas of necrosis. The pathologic changes in the thoracic and abdominal viscera are limited to congestion, edema, and hyperplasia of the lymph nodes and spleen (Wesselhoeft, Smith, and Branch). No intranuclear inclusion bodies have been described in man but they are occasionally present in experimental animals (Hurst).

Causal Agent. The virus of equine encephalomyelitis is pathogenic for mice, guinea pigs, calves, sheep, dogs, and rabbits. In most of these animals there is, after intracerebral inoculation, a rapidly fatal disease, with death in from three to five days. The pathologic changes are identical with those in man, and in the experimental animals there is no histologic difference between the eastern and

western strains of the virus. In the guinea pig an interstitial pneumonia is occasionally observed. Although the clinical disease and the viruses of eastern and western equine encephalomyelitis, of Borna disease, and of an *equine disease in Brazil and Venezuela* are similar, there are immunologic differences in the five viruses (Gordon). Specific neutralizing bodies appear in the blood of man and of experimental animals in from seven to ten days after the onset of the disease. The virus grows well on the chorio-allantoic membrane of the chick embryo and a successful vaccine

with the intense inflammatory process in the brain and spinal cord, the onset of the disease is sudden, especially in children, and the clinical symptoms and signs are commanding. The pathologic changes affect all parts of the brain, and there are therefore few localizing signs. The foci of necrosis represent irreparable damage to the brain and there are therefore many residual signs and symptoms in the few persons who recover.

Venezuelan Equine Encephalitis. The virus of equine encephalomyelitis in Venezuela is distinct from that in the United States. Labo-

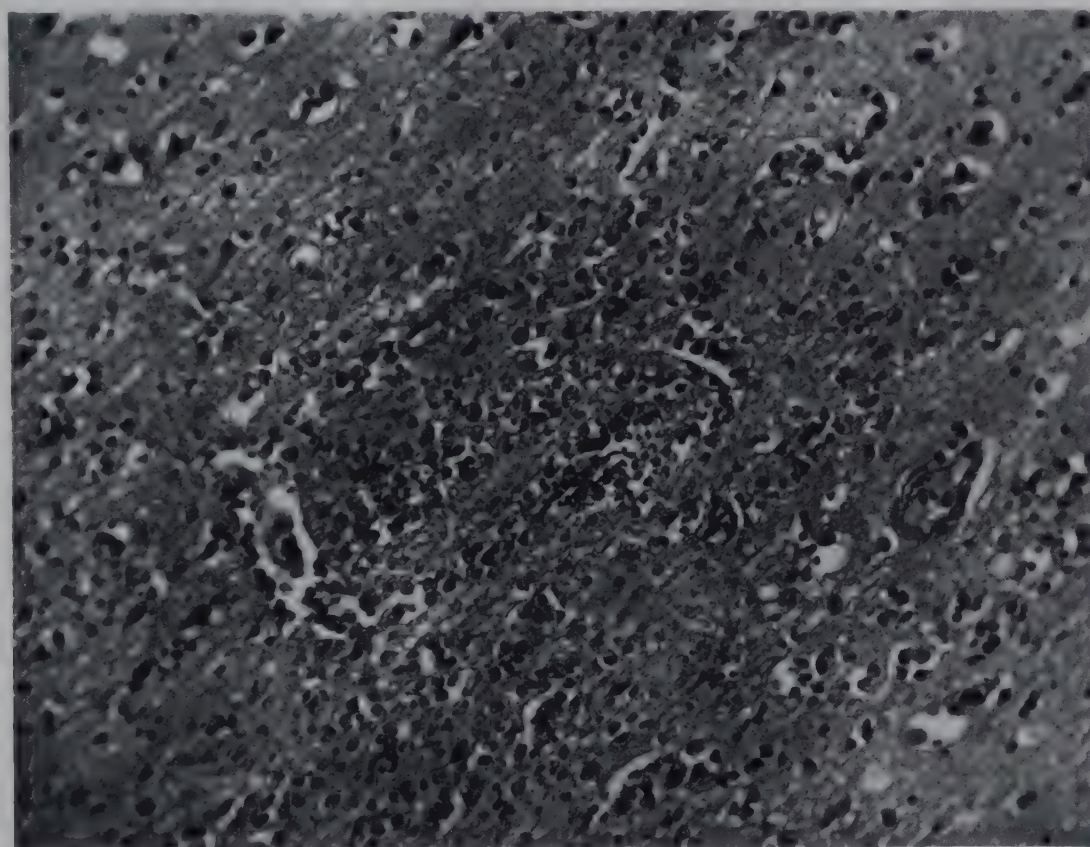


Fig. 210. Brain in equine encephalomyelitis. (Tissue by courtesy of Dr. Sidney Farber.)

has been prepared by this method (Eichhorn and Wyckoff).

Transmission. In the course of the epidemic in Massachusetts it was noticed that mosquitoes were extremely prevalent and that many human patients had never come in contact with a diseased horse. Although it has not been proved that the mosquito is the natural vector of the disease, it has been shown that a considerable number of mosquitoes, particularly *Aedes sollicitans*, a native of the Atlantic seaboard, are capable of transmitting the virus from one guinea pig to another. The tick, *Dermacentor andersoni*, may also be a vector. Ring-necked pheasants may die of the disease (Tyzzer, Sellards, and Bennett), and the conviction is growing that birds are the natural reservoir of the virus.

Clinicopathologic Correlation. In keeping

ratory infections are common, and the virus has in two instances been recovered from the nasopharynx, suggesting the possibility of direct contact or air-borne infection (Lennette and Koprowski).

Lymphocytic Choriomeningitis

Pathologic Anatomy. This disease is seldom fatal, and only a few pathologic studies in man are available. The brain is congested and edematous. The meninges are infiltrated with lymphocytes and a few mononuclear cells, and this infiltration extends into the cerebral substance in the perivascular spaces, especially in the white matter. About small blood vessels there are eccentric foci of gliosis. There are numerous swollen ganglion cells with small cytoplasmic inclusion bodies. All parts of

the brain are affected, but the changes are more advanced in the cerebral hemispheres (Smadel, Green, Paltauf, and Gonzales).

In experimental animals, particularly in mice, the pathologic changes are essentially those of a mild meningitis. The meninges and the choroid plexus are infiltrated with a moderate number of cells, predominantly lymphocytes, but mononuclear cells, plasma cells, and polymorphonuclear leukocytes are occasionally found. There is little if any fibrin in the subarachnoid space. The astrocytes immediately beneath the ependyma of the ventricles may proliferate. There is no cellular infiltration into the brain substance and no evidence of degeneration of ganglion cells, except in an occasional Purkinje cell.

In the viscera in man there are occasional small foci of necrosis and lymphocytic infiltration in the adrenal, liver, and kidney. The spleen is slightly enlarged and shows the usual hyperplasia associated with infectious diseases. In the lung there are small foci of interstitial pneumonia, similar to those observed in association with influenza and pertussis (Findlay and Stern).

Causal Agent. The virus in lymphocytic choriomeningitis, in contrast with that in most viral diseases of the central nervous system, is present in the spinal fluid, and may be easily recovered by intracerebral inoculation into mice (Scott and Rivers). Within a week after the development of clinical symptoms, neutralizing bodies and complement-binding bodies may be demonstrated in the blood.

Transmission. No information is available on the exact method of transmission, since only isolated cases have been observed.

Clinicopathologic Correlation. The clinical symptoms and signs are those of a mild infectious disease: malaise, generalized aching, and fever; and of slightly increased intracranial pressure: headache, vomiting, drowsiness, and moderately active reflexes. The spinal fluid is under increased pressure and contains rarely over 2000 cells, principally lymphocytes.

Acute Aseptic Meningitis of Wallgren. Many years before the original description of lymphocytic choriomeningitis, Wallgren described a condition called acute aseptic meningitis, characterized by a sudden onset of meningeal symptoms associated with an increase of lymphocytes in a bacteria-free spinal fluid; a benign course with no compli-

cations, the absence of a focus of acute or chronic infection in the vicinity of the brain; and the absence from the community of a disease known to be capable of producing irritation of the meninges (Wallgren). According to immunological tests a certain percentage of these cases are really lymphocytic choriomeningitis, but it should be emphasized that the two diseases are not identical (Baird and Rivers).

Pseudolymphocytic Choriomeningitis. A virus has been isolated from two patients with signs and symptoms similar to those of lymphocytic choriomeningitis, which does not have the same properties. Little else is known (MacCallum, Findlay, and Scott).

Swineherd's Disease of Bouchet. In Europe there is a disease among swine and swineherds similar to lymphocytic choriomeningitis, but according to immunologic tests it is caused by a distinct virus (Durand, Giroud, Larrière, Mestrallet, Bouchet).

Miscellaneous Neurotropic Viral Diseases

Louping Ill. This is a natural disease of sheep in Scotland and rarely of man. The pathologic changes are those of a diffuse encephalomyelitis with specific destruction of the Purkinje cells of the cerebellum.

Miscellaneous Neurotropic Viruses. A number of immunologically distinct viruses have been isolated from mosquitoes in Africa, South America, and the United States. In some instances neutralizing antibodies against the virus have been identified in the serum of man, but the various diseases are not well understood (Olitsky and Casals).

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LI

Diseases of Unknown Cause with Reactions Similar to Those of Bacterial and Viral Diseases

Unfortunately the causes of many interesting and important diseases are still unknown. One group is characterized clinically by signs and symptoms pointing to an infection, and anatomically by inflammation similar to that resulting from the action of bacteria and viruses. Despite the most diligent study no proved cause has been demonstrated by cultural methods or by animal inoculation. Discussion here may serve to focus attention on these diseases, and stimulate investigation.

Lethargic Encephalitis

In the winter of 1916–1917 there first appeared in Vienna a disease which has come to be known as “lethargic encephalitis” (Economo). In the succeeding years sporadic and edemic cases appeared throughout the world.

Pathologic Anatomy. The brain and spinal cord are edematous and hyperemic, and there are occasional small foci of hemorrhage about the third ventricle, aqueduct of Sylvius, and in the brain stem. There is inflammation of the entire central nervous system. In many instances the most severe alteration is in the mesencephalon involving the nuclei and white matter of the striate body, the nuclei adjacent to the third ventricle, the substantia nigra, and the nuclei of the cranial nerves in the pons and the medulla. There is infiltration into the spaces of Virchow-Robin with lymphocytes and a few mononuclear cells and plasma cells. There is a similar but less severe infiltration directly in the substance of the brain, which is edematous. The ganglion cells in an involved area show chromatolysis and necrosis with prominent neuronophagia. The blood vessels

throughout are dilated, and there are frequent hemorrhages into the space of Virchow-Robin and into the nervous tissue. There is slight proliferation of the oligodendroglia and of the astrocytes (Buzzard and Greenfield; Macnalty). Inclusion bodies, not unlike those of herpes, have been observed in ganglion cells and in glial cells (Dawson). The meninges show slight edema and infiltration with lymphocytes.

Causal Factors. In spite of numerous attempts, no virus or bacterium has been shown to cause lethargic encephalitis. The virus of herpes has been isolated from the brain tissue of eight cases of lethargic encephalitis. But it has also been isolated from the spinal fluid and from the brain of persons with other diseases (Flexner and Amoss). Both lethargic encephalitis and herpes appear to be secondary diseases. It is possible that some other disease prepares the ground for the action of a secondary or indigenous virus (Zinsser).

Transmission. It is difficult to establish lethargic encephalitis as a disease transmitted from person to person. More than one case in a family is unusual. Rarely there are definite epidemic foci (Smith).

Clinicopathologic Correlation. There are two groups of symptoms and signs in lethargic encephalitis: (1) the general symptoms, somnolence, stupor, and fever, and (2) localizing symptoms dependent upon destruction of ganglion cells in certain parts of the central nervous system. These latter occur in infinite combinations dependent upon the specific localization in any given case.

Sequelae: Parkinsonian State. During the course of the acute disease there is a mortality of about 25 per cent, but about 95 per

cent of those who recover have some permanent damage to the nervous system, varying from paralysis of a single ocular muscle to complete insanity, resulting from the widespread destruction of ganglion cells (Duncan). The sequela of greatest interest is the parkinsonian state, characterized by rigid posture, expressionless face, retardation of voluntary movements, hypertonia, and tremor, without signs of a lesion of the pyramidal tract. This is apparently associated with destruction of the ganglion cells in the substantia nigra (Hassin and Bassoe; McAlpine).

Herpes Zoster

Pathologic Anatomy. The characteristic pathologic changes of herpes zoster are found in two regions: the skin, and the cranial and spinal ganglia. In the skin there are vesicles identical in gross and microscopic structure with those of herpes simplex. The changes in the ganglia are: hemorrhage, infiltration with lymphocytes and a few leukocytes, and destruction of ganglion cells, followed in from two to three months by fibrosis of a part or all of the ganglion. As a result of the loss of ganglion cells there is degeneration, easily demonstrated by the Marchi method, of the peripheral nerve, the dorsal root, and isolated fibers in the substantia gelatinosa. The lesions in the skin correspond to the peripheral distribution of the cells within the involved ganglion. According to the exhaustive studies of Head and Campbell in a large series of cases, the ganglia which receive afferent impulses from the viscera through the white rami of the sympathetic system are those most commonly affected. The lymph nodes through the body are enlarged, edematous, and congested.

Causal Factors. A definite virus has not been isolated from herpes zoster (Cole and Kuttner). The disease has been observed after trauma to the vertebrae, to the peripheral nerves, to the skin, and to the cornea (Klauder). In guinea pigs, inoculation of the virus of herpes simplex into previously tarred skin results in the pathologic picture of herpes zoster, suggesting a relation of the two (Teague and Goodpasture).

Transmission. In the absence of a known causal agent it is difficult to define the methods of transmission of a disease. The epidemicity of herpes zoster would, however,

suggest that it is transmitted from person to person.

Clinicopathologic Correlation. As the result of the inflammation in the ganglia there are hyperalgesia and pain over the area of distribution from the ganglion. The vesicles in the epidermis are also probably to be explained at least in part by the central changes. When motor fibers are intimately associated with a ganglion, there is paralysis of a focal region; for example, facial paralysis when the geniculate ganglia is affected. Despite the destruction of ganglion cells, there is rarely any permanent disability, and complete recovery is to be expected.

Polyradiculoneuritis

In a very few patients, sometimes following any one of a variety of upper respiratory infections, a peculiar type of polyneuritis develops.

Pathologic Anatomy. The peripheral nerves are slightly enlarged and edematous. There are degeneration of the myelin sheaths and fragmentation of the axis cylinders, without histologic signs of inflammation. In the dorsal root ganglia the neurons show varying degrees of degeneration, with slight to moderate lymphocytic infiltration. The spinal cord, brain, and meninges are typically normal, both grossly and microscopically. In at least some cases there are definite changes in the viscera: focal necrosis, slight cellular infiltration in the liver, adrenals, and heart, and a necrotizing type of arteritis and phlebitis (Sabin and Aring).

Causal Factors. Cultures and animal inoculation have uniformly given negative results for the presence of a micro-organism (Sabin and Aring).

Clinicopathologic Correlation. The degeneration of the peripheral nerve leads to paralysis and paresthesia. Involvement of the seventh cranial nerve is common. In the spinal fluid there is a significant increase in protein, with only a slight increase in cells. The mortality is about 15 per cent (Gilpin, Moersch, and Kernohan). In most who recover there is complete restoration to normal, but occasionally residual signs and symptoms are noted, and anatomically there is degeneration of the dorsal roots and of the dorsal white columns (Russell and Moore).

Primary Atypical Pneumonia

During the 1940's clinicians observed an increasing number of patients with a lower respiratory infection which did not seem to fit into any recognized category. The great majority of cases occurred in young adults grouped together in schools and Army camps.

Pathologic Anatomy. Primary atypical pneumonia is a clinical syndrome and not a disease entity, hence the pathologic anatomy

in institutions may reach 15 per cent, and is usually high in doctors and nurses (Young, Storey, and Redmond).

Clinicopathologic Correlation. The pathologic changes and the clinical signs and symptoms are not correlated. The evidence of infection of the respiratory tract, in decreasing order of frequency, are cough, fever, headache, malaise, chilliness, coryza, and sore throat. The incubation period is probably seven to twenty-one days. The mortality is



Fig. 211. Polyradiculoneuritis. *A*, Cellular infiltration in a nerve of the cauda equina. *B*, Necrotizing lesion of small pial artery of spinal cord.

varies from patient to patient. In general, the lungs show a firm, dark red, irregular consolidation. The alveolar walls and the peritruncal tissues are hyperemic, and are infiltrated with mononuclear cells, lymphocytes, plasma cells, and a few leukocytes. Within the alveoli there is an exudate of mononuclear cells, eosinophils, leukocytes, fibrin, and red blood cells. The bronchi are filled with leukocytes (Dingle, Abernathy, Badger, Buddingh, Feller, Langmuir, Ruegsegger, and Wood).

Causal Agent. Many attempts have been made to isolate a virus or bacterium, but there is no agreement on those that have been isolated as the specific causal agent (Horsfall).

Transmission. No definite information is available on the mode of transmission. Infectiousness is not great, but the incidence rate

less than 1 per cent. The course may extend in mild cases from two to three weeks, and in severe cases up to eight or ten weeks. There is a characteristic cold agglutination (Meiklejohn).

Boeck's Sarcoid

Boeck's sarcoid is a chronic granuloma, persisting often for years, sometimes spreading slowly from organ to organ, frequently relapsing, seldom producing constitutional symptoms, resistant to treatment, and at times healing spontaneously (Longcope and Pierson).

Distribution of Lesions. Any organ or tissue may be involved, but there is a predilection for the skin, lymph nodes, lungs, and bones.

Typical Lesion. The essential lesion of Boeck's sarcoid is a firm, pearly gray, semi-translucent, spherical or flat nodule, occurring discretely or as confluent masses. Large,

cells with peculiar basophilic cytoplasmic inclusions. Typically there is no central caseation, or peripheral infiltration with lymphocytes as in the tubercle. Growth proceeds

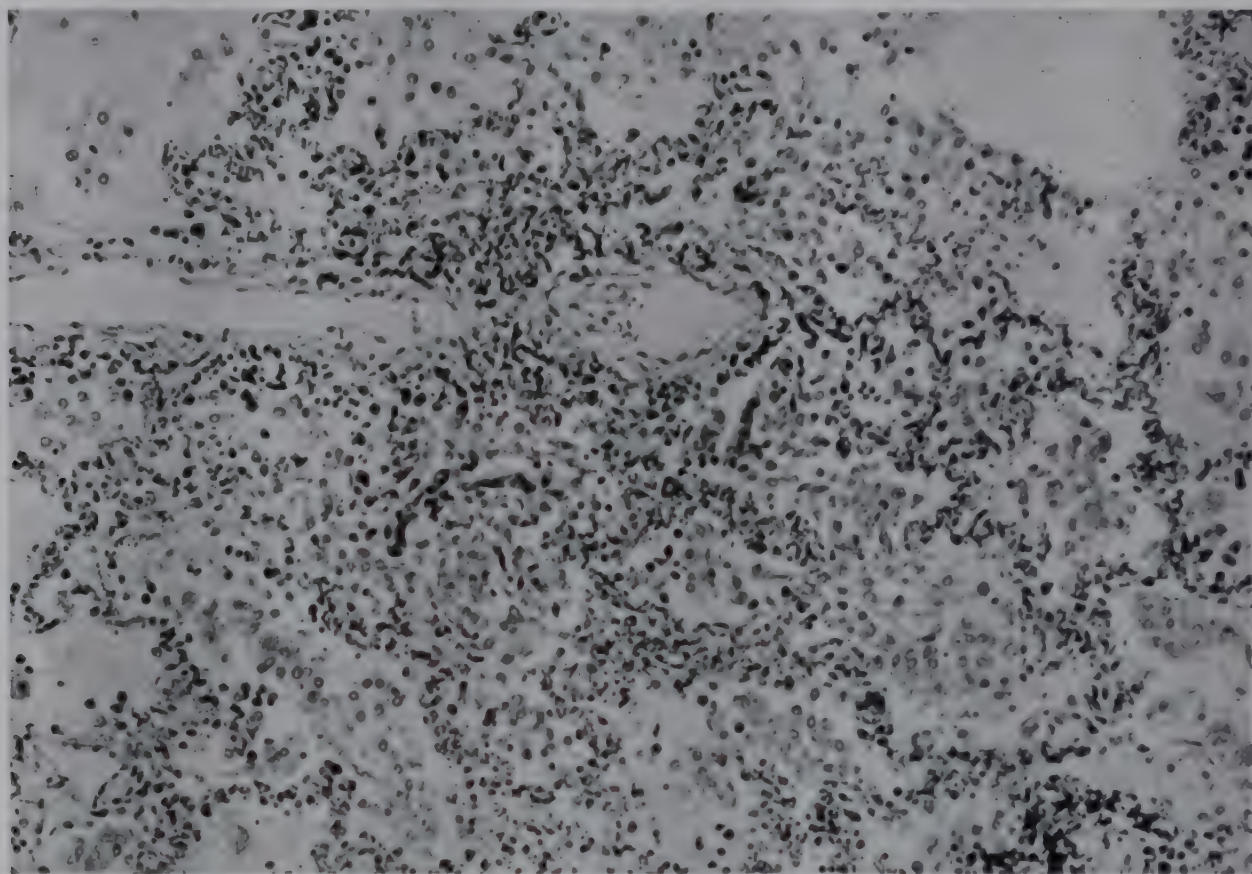


Fig. 212. Primary atypical pneumonia. (Slide by courtesy of Armed Forces Institute of Pathology, Major Alfred Golden, Acc. No. 85688.)



Fig. 213. Boeck's sarcoid. *A*, Foci of rarefaction in short bones of hand. (Armed Forces Institute of Pathology, Neg. No. 73721). *B*, Focal lesion in skin.

pale-staining, polygonal or spindle-shaped, epithelioid cells are arranged irregularly or regularly to form a tubercle. In the center or eccentrically there may be large irregular giant

apparently by formation of new nodules, and not centrifugally. Healing proceeds by resolution or by fibrosis (Longcope).

Incidence and Course. Sarcoid begins in

early adult life, affects both sexes and both the white and the colored races. It is rare in children (Hannesson).

Causal Factors. The similarity of the lesion to that of tuberculosis has led many to believe that sarcoid is some atypical form of tuberculosis (Pinner). However, until tubercle bacilli can be demonstrated with more regularity, it is best to withhold judgment.

Clinicopathologic Correlation. Lesions of the lungs appear on radiographs as a reticular infiltration, most conspicuous about the hilum. The osseous lesions cause focal resorption of

edematous and hyperemic and infiltrated with mononuclear cells, plasma cells, and leukocytes. Within the mononuclear cells, there are numerous small Donovan bodies. As the nodule enlarges, the epithelium becomes thin and is eventually lost. Confluence of nodules and necrosis of the superficial layers produce the characteristic serpiginous ulcer. With further progression the tissue of the dermis proliferates rapidly, and exuberant granulations project onto the surface. At the edges of the ulcer, there is epithelial proliferation. Within the granulation tissue are numerous plasma

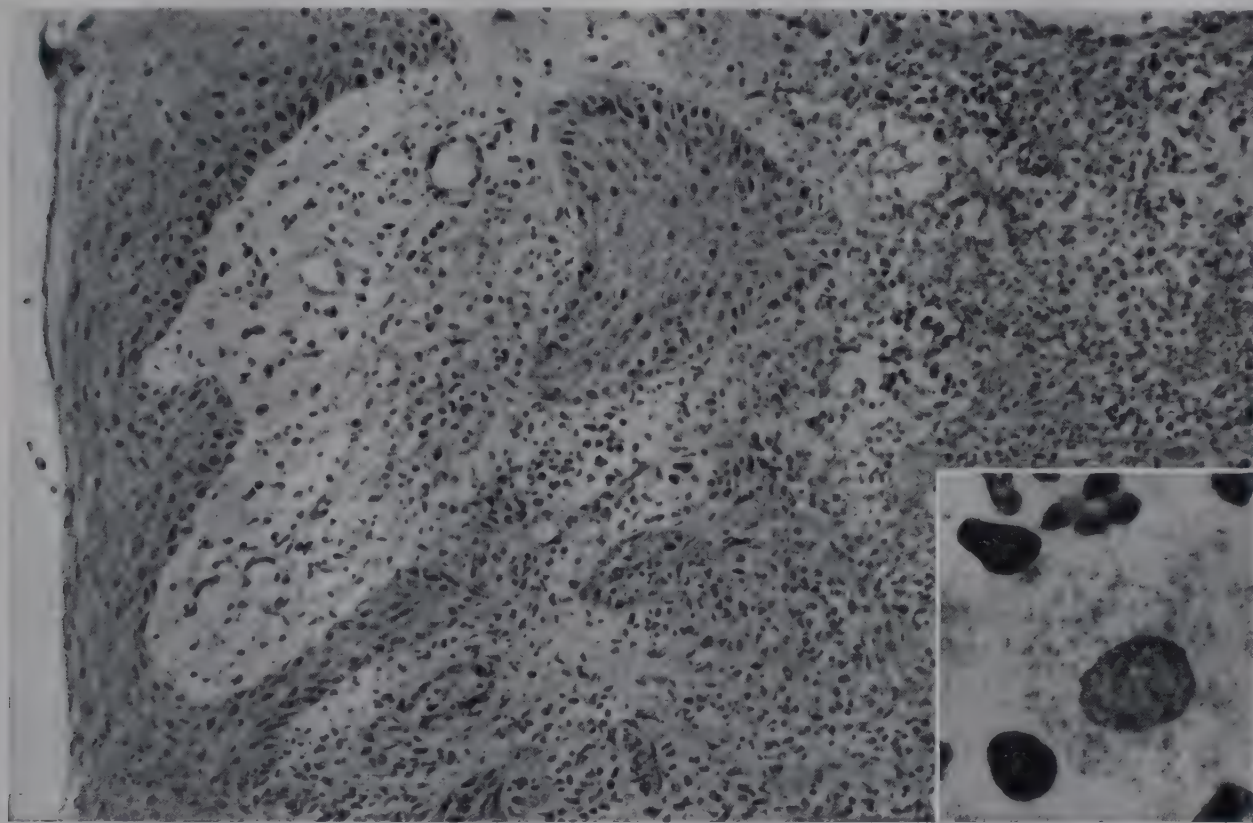


Fig. 214. Inguinal granuloma of vulva to show inflammatory reaction and, in the insert, the Donovan bodies. (Armed Forces Institute of Pathology, Neg. No. 71637 and 71662.)

bone, so that there are punched-out foci of radiolucence in the ends of the phalanges—one of the most important diagnostic signs of the disease. Involvement of the heart may cause disturbances of conduction and cardiac failure (Longcope and Fisher), involvement of the lung, cough and dyspnea. Affection of the parotid and lacrimal glands is one cause of Mikulicz's syndrome. A significant number of patients have a falsely positive Wassermann reaction. An unexplained increase of plasma globulin to 3 to 6 gm. per 100 cc. is a useful diagnostic sign.

Inguinal Granuloma

Pathologic Anatomy. The initial lesion of inguinal granuloma is a small nodule in the skin. The epithelium is intact, and the dermis

cells, many mononuclear cells with Donovan bodies, and a few leukocytes, but no lymphocytes. Healing proceeds slowly by cicatrization of the granulation tissue and reepithelization of the surface. The deeper ulcers may become secondarily infected with spirochetes, fungi, and pyrogenic bacteria (D'Aunoy and von Haam).

Systemic Lesions. Focal inflammatory lesions and abscess may be observed in bones, joints, liver, lungs, spleen, intestine, and internal female genitalia. The typical cell is a foamy mononuclear cell containing many Donovan bodies (Lyford, Johnson, Blackman, and Scott).

Causal Factors. The Donovan bodies can be cultured in the chick yolk sac (Anderson) and on artificial media, but these cultured organisms are not pathogenic for man (Dienst;

Chen, and Greenblatt). Infection of sterile pus from a bubo will cause the disease in man after an incubation period averaging forty-five days. An antigen, useful in complement-fixation tests, can be prepared from cultures (Dunham and Rake).

Clinicopathologic Correlation. Inguinal granuloma is largely a disease of Negroes. The exact method of transmission is unknown, but the frequency of lesions in the pudendal region suggests venereal contact.

Miscellaneous Diseases

From time to time new diseases are described, of which the signs and symptoms suggest an infectious nature. Some are discussed here in the hope that clinicians and pathologists will undertake anatomic and causal studies with biopsy material.

Scleroma. This condition most common in the nose—rhinoscleroma—also occurs in the pharynx, larynx, and trachea. The mucosa is thickened by discrete and confluent nodules 1 to 10 mm. in diameter; at first it is soft but later hard. The characteristic microscopic feature is a large foam cell containing small bacilli. The clinical course is benign and the duration may be up to twenty or thirty years (Cunning and Guerry).

The small bacillus, *Klebsiella rhinoscleromatis*, is probably the causative agent, but this has been questioned (Levine, Hoyt, and Peterson). The disease occurs in all parts of the world and multiple instances in a family are recorded.

Primary Pneumonia in Newborn Infants. In the winter of 1941 a peculiar respiratory infection of newborn infants occurred in Minneapolis. Since then other outbreaks in various parts of the United States have been reported. In the lungs there is bronchitis and interstitial pneumonitis. Within the bronchi and in some of the alveoli there is an infiltration with mononuclear cells. The bronchial epithelium is desquamated and necrotic. The most characteristic feature is the occurrence of acidophilic, cytoplasmic inclusion bodies, varying from 3 to 6 microns in diameter, each surrounded by a clear halo. The inclusion bodies can be demonstrated in a smear of the nasopharyngeal secretions. Attempts to isolate a virus by inoculation of many species of animals have failed. The pathologic changes

are directly related to a typical clinical syndrome of cough, cyanosis, dyspnea, and fever. The mortality is 20 per cent (Adams, Green, et al.).

Pleurodynia. This clinical syndrome has long been known. It occurs in epidemic form among children and young adults, and is characterized by fever and severe pain in the upper abdomen and lower thorax, lasting from twenty-four to forty-eight hours. Pleurisy or meningo-encephalitis is occasionally clinically demonstrable (Howard, Weymuller, Edson, Ittner, Watson, and Cassidy).

Epidemic Nausea and Vomiting. Widespread outbreaks of nausea and vomiting in association with upper respiratory infection have been reported from many places. The incubation period is two to seven days. The clinical signs—nausea, vomiting, vertigo, headache, diarrhea, and pyrexia—last from one to two days (Bradley).

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LII

Complex Infections

In the early days of bacteriology, the recovery of a single bacterium from a disease and the reproduction of this disease with cultures of the bacterium led to the formulation of Koch's postulates. Thus, the concept was developed that diseases were due to a single definite causal agent—a bacterium, a virus, or a protozoan parasite. In certain instances this concept is not adequate, and in the field of plant and animal pathology a number of diseases have been studied in which it is clear that two agents are operative. In distinction from mixed infections where two bacteria are by chance present in a pathologic lesion, those infections where this is a causal relation of the two agents are known as "complex infections." Although only one human disease of this type has been described, the principles involved are of sufficient importance to justify a short description in a textbook of human pathology. The more important of these diseases are blackhead of turkeys, rugose mosaic of potatoes, streak of tomatoes, swine influenza, type III coryza of fowls, breaking of tulips, and infectious myxomatosis of rabbits.

Blackhead of turkeys is an example of a disease produced by a metazoan and a protozoan parasite. Rugose mosaic of potatoes is caused by the synergistic action of two viruses. Swine influenza is the result of a bacterium and a virus, and tulip breaking results from the antagonistic action of two viruses (Shope).

Swine Influenza

Coincident with the pandemic of influenza in 1918 there was an epizootic disease of swine which, because of the similarity, both clinically and pathologically, to human influenza, was named swine influenza. The morbidity in an infected herd is high and practically all animals under one year of age be-

come sick. The principal symptoms are fever, anorexia, prostration, cough, leukopenia, and rapid respiration. Illness lasts from two to six days and the mortality may be as high as ten per cent (Shope).

In 1928, when the first investigations of the disease were initiated, the bacterium *Hemophilus influenzae suis* was isolated from the lungs of practically every case. Attempts to reproduce the disease in swine with this bacterium had erratic results. In a few experiments, typical swine influenza followed intranasal inoculation of cultures of the organism, but most experiments were fruitless. The swine showed no signs or symptoms, and pathologic examinations on the third to fifth day showed no lesions. On the other hand, intranasal instillation of a filtrate of ground-up lung tissue produced a mild disease of swine, characterized by a fever for two or three days, and complete recovery. If the animals were killed during the period of pyrexia, only slight inflammation of the pharynx and trachea was found. There were no lesions in the lung similar to those in naturally occurring swine influenza.

The anomalous conclusion was that a bacterium was uniformly present in the lungs of sick swine which did not reproduce the disease, and that a virus was also present in the lungs which, when inoculated into swine, produced another disease which was named "virus-disease of swine." It then occurred to Shope to inoculate a single animal with both the bacterium and the virus. There resulted typical swine influenza. The experiment has been repeated many times and leaves no doubt that influenza in swine is the result of the combined action of two agents. The reservoir of the virus is the lung worm of swine (Shope). There is a similar synergistic action of the bacterium and virus in chick embryos (Bang).

Similar experiments cannot be carried out in man, but the preponderance of evidence at the present time is that human influenza is caused by two agents, a virus and a bacterium. It is probable that in human influenza the bacterium is not fixed; in other words, that in some cases it is the combined action of the virus with *Hemophilus influenzae hominis*, in others with *Streptococcus hemolyticus*, and in still others with *Diplococcus pneumoniae*.

Progressive Bacterial Synergistic Necrosis

This condition, also known as "progressive bacterial synergistic gangrene" and "phagadenic ulcer," typically begins in the skin about a wound draining a deeper infection, such as appendicitis or empyema. The affected region is at first swollen and red. Later there is induration, and the redness and swelling spread centrifugally. The center turns purple, and with the onset of necrosis is a dirty grayish brown color. Finally the center liquefies and the base of the ulcer is composed of granulation tissue. In the well developed lesion there is then a peripheral circular zone of red, swollen tissue. Next centrally is a zone of purple, irregularly but sharply delineated from the next central zone of dry dark brown or black necrosis. In the center is a soft granulating tissue, extending down to the deep fascia. Within the red and purple zone there are edema, dilatation of vessels, and an intense infiltration with leukocytes. The epithelium in this region is edematous and thickened (Lichtenstein).

Causal Agents. From most cases both a

micro-aerophilic, nonhemolytic streptococcus and an aerobic staphylococcus can be isolated. By simultaneous injection of pure cultures of these organisms, an identical lesion has been produced in animals (Brewer and Meleney).

Clinicopathologic Correlation. Although most cases occur in and about surgical wounds, some apparently start as a primary infection of the skin. Unless treated radically by complete excision and application of zinc peroxide, the ulcer continues to spread until death.

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LIII

Diseases Caused by Fungi

The diseases caused by pathogenic fungi and yeasts are of great interest to the dermatologist because most of them involve structures associated with keratin—that is, the skin, the hair, and the nails. On the other hand some of the fungi and yeasts, despite the fact that they enter through the skin, are capable of invading the body and causing lesions in all of the viscera. A few of the fungi gain entrance through the respiratory or alimentary tract.

Systematic Position of the Fungi. The fungi and yeasts are collectively known as “Eumycetes,” and represent plants higher in the evolutionary plane than the bacteria, or Schizomycetes. The systematic classification of the Eumycetes has been the subject of great controversy, but in general four classes are recognized: Hyphomycetes, Ascomycetes, Phycomycetes, and Basidiomycetes. The Hyphomycetes are also known as “fungi imperfecti”; there are no asci (sacs containing spores) in the fruiting stage, and the mycelium is septate. The Ascomycetes have asci and the mycelium is septate. Phycomycetes have no asci, and the mycelium is nonseptate in the vegetative stage.

General Types of Reaction of Tissue to Fungi. It is convenient to classify the fungal diseases on the basis of the extent of the invasion of the body. Three types are recognized: superficial, parasitic, and subcutaneous or systemic. In the *superficial* variety the fungi are limited by the surface of the body, and grow and develop in what is, in reality, the environment. There is little inflammatory reaction in the underlying tissues. In the *parasitic* variety the organism invades the body to a limited extent. The surrounding tissue exhibits in general an acute inflammation, characterized by infiltration with polymorphonuclear leukocytes. In the more severe types there are necrosis and suppuration immedi-

ately adjacent to the superficially placed fungi. In the *subcutaneous or systemic* variety the organisms may be identified in the dermis, in the subcutaneous tissues, or in the viscera. The lesions in general are those of an infectious granuloma, composed essentially of a necrotic center surrounded by a zone of proliferation of epithelioid cells and fibroblasts and the formation of giant cells. The giant cells frequently contain the fungus and are to be regarded as foreign body giant cells.

Superficial Dermatomycoses

In the four superficial dermatomycoses—pityriasis versicolor, erythrasma, piedra, and trichomycosis—the fungi grow entirely on the surface of the body, and there is little or no inflammatory reaction in the tissues.

Parasitic Dermatomycoses

Epidermophytosis. This condition, commonly known as “athlete’s foot,” may appear in a variety of forms, the most common of which are the vesicular, scaling, macular, macerated, and fissured types.

Pathologic Anatomy. The lesions are found most commonly on the toes, but are not uncommon on the fingers, thighs, palms, soles, and axillae (Fig. 215). The initial lesion is an intra-epidermal vesicle in the prickle cell layer. The walls of the vesicle are made up of the surrounding epidermis, and the roof consists of a few layers of the stratum granulosum and the keratinized layer. The vesicles contain fibrin, polymorphonuclear leukocytes, and necrotic epithelial cells. Adjacent to the vesicles there is parakeratosis and migration of polymorphonuclear leukocytes into the epidermis. In the dermis there are edema, hyperemia, and infiltration with polymorphonuclear leukocytes and lymphocytes. In

chronic cases there is dermal fibrosis. Fungi are demonstrated with difficulty (Peck).

Dissemination. In general the fungus causing epidermophytosis is transmitted from man to man on dirty clothes, old suspensories, and on the floors of locker rooms and shower baths.

Causal Agent. There are at least three different fungi responsible for athlete's foot in the United States: *Epidermophyton inguinale* (floccosum), *Trichophyton interdigitale*, and *Trichophyton rubrum*. At least eighteen other species, including *Blastomyces*, have been

cytes. After some days or weeks there is a proliferation of fibroblasts. In the *deep variety* the fungi are found on the hair follicles and produce a folliculitis and perifolliculitis. The hairs become brittle and break off at the surface of the skin or within the follicle. There is invasion of the epithelium of the follicle with polymorphonuclear leukocytes, and the entire area undergoes necrosis with the formation of an abscess connected with the surface through the former hair shaft. About the region there is proliferation of fibrous tissue, and on occasion the formation of abscesses



Fig. 215. Epidermophytosis of interdigital spaces of fingers. (Photograph by courtesy of Dr. Morris Moore.)

isolated from similar lesions. The organisms are most readily identified by placing the scraping of the lesions in strong sodium hydroxide (Weidman).

Epidermophytids. In some persons with an epidermophytosis of the toes, small papular lesions appear on the fingers and backs of the hands, which may constitute an allergic response to the infection on the feet or metastatic lesions (Peck).

Trichophytosis. Trichophytosis includes Celsus's kerion and ringworm of the beard or parasitic sycosis. There are two types of the disease, superficial and deep.

Pathologic Anatomy. In the *superficial variety* there is parakeratosis with the formation of small intra-epidermal vesicles containing serum and polymorphonuclear leukocytes. In the dermis there are a varying degree of edema and infiltration with leuko-

not connected with the surface. The deep variety is most often caused by the ectothrix and neo-endothrix classes of *Trichophyton*.

Dissemination. Most cases of ringworm of the beard and other types of *Trichophyton* infection are transmitted from man to man through such objects as razors and hair brushes, or from animals to man.

Causal Agent. Immunity. Trichophytids. Within the *Trichophyton* there are several genera and many species. The more important are *Trichophyton gypseum*, *Trichophyton tonsurans*, and *Trichophyton flavum*. Agglutinins against the organism are developed. The trichophytid is similar to the epidermophytid.

Microsporiasis. Microsporiasis is the characteristic and well known ringworm of the scalp occurring most commonly in children. The pathologic changes are similar to those

of trichophytosis. The fungi enter the hair follicles and set up a purulent perifolliculitis. The fungi are disseminated through inanimate objects, and boys are apparently far more susceptible than girls. The common organism in man is *Microsporum audouini*, but man is susceptible to similar organisms of the dog, cat, and horse. The organism when present on the hair is fluorescent, and this property is useful in diagnosis.

It is apparent that "ringworm," as a general term, should be abandoned in favor of "trichophytosis" for ringworm of the beard, "microsporiasis" for ringworm of the scalp, and "epidermophytosis" for ringworm of the body.

Favus. In favus large scutula are formed on the surface of the scalp. These are biconvex, round masses of fungi and necrotic cells. The epidermis immediately beneath is atrophic, and the dermis is edematous, hyperemic, and infiltrated with lymphocytes and polymorphonuclear leukocytes. Immediately adjacent to the scutulum the epidermis shows acanthosis. In severe cases the epidermis is completely destroyed, and the mass of fungi rests directly on the inflamed dermis.

Tinea Imbricata. This is a disease of the Malay Peninsula and the islands of the South Pacific, characterized grossly by small round or oval, slightly raised, dark brown patches that continue to grow concentrically, leaving a characteristic interlacing network of lines. There is a mild inflammation in the dermis, and parakeratosis and acanthosis in the epidermis. The causative organism is known as *Endodermophyton concentricum*.

Moniliasis

Bronchomoniliasis. The condition known as "bronchomoniliasis" is an infection of the lung and smaller bronchi with fungi of the genus *Monilia* (or *Candida*).

Pathologic Anatomy. The pathologic changes are essentially those of tuberculosis. Throughout the lung, but more especially in the upper lobe, there are small and large cavities, surrounded by connective tissue. In the immediately adjacent lung substance, and at times through the entire lung, there are small, yellow, soft nodules, approximately 1 mm. in diameter, similar in gross appearance to the tubercle. Each nodule is composed of a

central mass of necrotic tissue, and a surrounding zone of epithelioid cells, giant cells, fibroblasts, and lymphocytes. Within the central necrotic focus, and to a less extent in the surrounding living tissue, there are monilial threads (Koerth, Donaldson, and McCorkle).

Causal Agent. Organisms of the genus *Monilia* are gram-positive, oval cells, ranging from 1 to 2 microns to 8 by 9 microns, which can be further identified by certain biological reactions. Strains isolated from human disease are pathogenic for guinea pigs and rabbits. Agglutinins and complement-binding bodies develop in man and in experimental animals, and serve to distinguish the pathogenic strains from the common yeasts (McKinney).

Clinicopathologic Correlation. The symptoms and signs are those of a destructive lesion of the lung. There is a productive cough and the same physical findings as in tuberculosis, depending on consolidation and cavitation of the lung. There are also the systemic signs and symptoms of an infectious disease, such as fever and malaise. Not all fungi found in the sputum are pathogenic, and great care is necessary to establish the relation of a given fungus to disease of the lung. It is said that fungi may be present in the sputa of about 3 per cent of all persons (Castellani). Tea-tasters' cough of India and Ceylon may be a bronchomoniliasis acquired by aspiration of the fungi on the dry tea leaves (Castellani).

Thrush. The lesions of thrush are found most frequently in the mouth and in the vagina, and less frequently on the skin.

Oral and Esophageal Thrush. Oral thrush is found most frequently in newborn infants, but is occasionally seen in older children, especially in association with debilitation. It is more common in artificially fed infants living in poor hygienic surroundings, and rarely develops without some previous injury or abrasion of the mucous membrane. The lesions are found on the margins of the tongue, on the inside of the lips and cheeks, and on the palate, as small, white patches, 1 to 5 mm. in diameter. When rubbed off, they leave small bleeding points. The mucous membrane generally is dry and red. The superficial layers of mucosa are destroyed, and the surface is covered with a membrane composed of the fungi, epithelial cells and necrotic tissue. The mycelia penetrate deeply into the wall. The capillaries of the adjacent submucosa are dilated,

and there is a moderate infiltration with polymorphonuclear leukocytes and lymphocytes. Identical changes may be present in the esophagus (Fig. 216). Occasionally small ulcerations, apparently caused by the same organism, are found in the small and large intestine (Ebbs).

Vaginal Thrush. Vaginal thrush is identical in appearance with oral thrush. It is most

on pathologic changes. The symptoms are those of a mild local inflammation.

Systemic Moniliasis. Under normal conditions it is unlikely that monilia of any sort invade the blood. However, on occasion, as in "main-line" drug addicts, the fungus may be introduced directly into the blood, causing lesions throughout the viscera and a vegetative endocarditis (Pasternack).



Fig. 216. Thrush of esophagus.

common in pregnant and in diabetic women. It affects the vagina and the cervix, and rarely the vulva (Liston and Cruickshank).

Thrush of the Skin. Following abrasions or in debilitated states the organism of thrush may produce an essentially similar disease on any part of the surface of the body.

Causal Agent. Most cases of thrush are caused by *Candida* (*Monilia*) *albicans*, but many different strains and varieties have been isolated from similar clinical and pathologic processes. Pure cultures of the organism have been used to produce the disease experimentally in both pregnant women and young children. Agglutinins develop in the blood stream, even after superficial infection. The organism evidently does not invade the body beyond the mucous membrane, and the mortality is low.

Clinicopathologic Correlation. The only signs are the lesions on the surface of the body, which have been described in the paragraph

Chromoblastomycosis (*Chromomycosis*)

Chromoblastomycosis, or dermatitis verrucosa, is caused by the fungus *Phialophora verrucosa* and other species of the genus usually called *Hormodendrum*. The lesions are usually on the feet and legs, and on the hands, wrists, and forearms. They begin as small nodules. Later ulceration and a discharge of yellow, thick pus occur. Within the pus are many brown, thick-walled, multilocular fungus cells. There are advanced hyperkeratosis and acanthosis, with thickening, broadening, and elongation of the interpapillary pegs. In the corium are discrete granulomatous lesions, showing central foci of polymorphonuclear leukocytes, lymphocytes, plasma cells, and eosinophils, with varying degrees of necrosis. Surrounding the central area are epithelioid cells, fibroblasts, and numerous giant cells. Within the giant

cells, or free in the necrotic debris, are the typical pigmented round organisms.

Sporotrichosis

Pathologic Anatomy. There are two forms of sporotrichosis, cutaneous and systemic. The nodules, both primary and secondary in the skin and along the lymphatics, are firm, at times softened, frequently ulcerated, and connected by firm fibrous cords (Fig. 217). The



Fig. 217. Sporotrichosis showing lymphatic spread. (Photograph by courtesy of Dr. Morris Moore.)

center of each nodule is composed of necrotic tissue, with a few surviving polymorphonuclear leukocytes, eosinophils, and monocytes. Surrounding the area of necrosis are numerous large epithelioid cells and abundant giant cells. At the periphery are fibrosis, increased vascularization, and infiltration with plasma cells and lymphocytes. The organism is difficult to demonstrate in the tissues. The systemic form of the disease, consisting of the formation of similar nodules throughout the viscera, is rare.

Causal Agent. *Sporotrichum schenckii* is moderately pathogenic for most laboratory

animals, either by subcutaneous or by intraperitoneal injection. Both agglutinins and complement-binding bodies are present in the blood stream in most cases. Sporotrichosis sometimes appears to be an occupational disease of gardeners, related to trauma from the thorns of plants.

Actinomycosis

Pathologic Anatomy. The general pathologic change in actinomycosis is the formation of numerous small discrete or confluent nodules of inflammatory tissue (Weed and Baggenstoss). In the center of each nodule are colonies of actinomyces, surrounded by a zone of liquefactive necrosis, with numerous polymorphonuclear leukocytes (Fig. 218). There is no distinct caseation, as in tuberculosis. About the area of liquefaction is a zone of granulation tissue infiltrated with leukocytes and a few giant cells. Peripherally there is a layer of dense fibrous tissue. Within the fibrous tissue or in the granulation tissue there may be foci of calcification.

Anatomic Types. A number of definite types of actinomycosis are recognized: cervicofacial, abdominal, pulmonary, cutaneous, pelvic, acute disseminated, and a miscellaneous group. In the *cervicofacial type* there are actinomycotic abscesses in the tissues about the jaw and neck. In the *abdominal type* there is great thickening by fibrous tissue of the ileocecal region, with numerous abscesses within the fibrous tissue, and fistulous tracts into the lumen of the intestine. This form frequently comes to the attention of the surgeon, and if the abdomen is opened, a permanent fistula is likely to result. In the *pulmonary type* the lesions—abscesses, proliferation of fibrous tissue and cavitation—resemble those of tuberculosis, except that there is no caseation. The *cutaneous type* gives rise to a superficial ulcerating lesion of the skin and subcutaneous tissues in which the yellow granules of the organism can be readily seen. Involvement of the *pelvic organs* is unusual except in association with one of the other types (Paalman, Dockerty, and Mussey). Isolated instances of actinomycosis of the *bone* and of the *central nervous system* (Moersch), and of *acute disseminated actinomycosis* have been reported.

Incidence. Actinomycosis is predominantly a disease of young men in the grain-raising areas of the world. The distribution suggests

that the organisms grow on the grain and penetrate the human body through some traumatic lesion. It has also been observed that some types of actinomyces, which under certain circumstances may become pathogenic, are present about the teeth of many persons, and occasionally in the gastro-intestinal tract.

Clinicopathologic Correlation. The typical course of actinomycosis lasts for many years, and the signs and symptoms depend on the

originally described in the United States by Gilchrist is now known as "North American blastomycosis." *Saccharomycosis hominis*, or "European blastomycosis," is the same disease as cryptococcosis, and will be described under that designation. Moore and others have shown that a group of diseases in South America, known as "South American blastomycosis," are caused by organisms which they placed in the genus *Paracoccidioides*, and

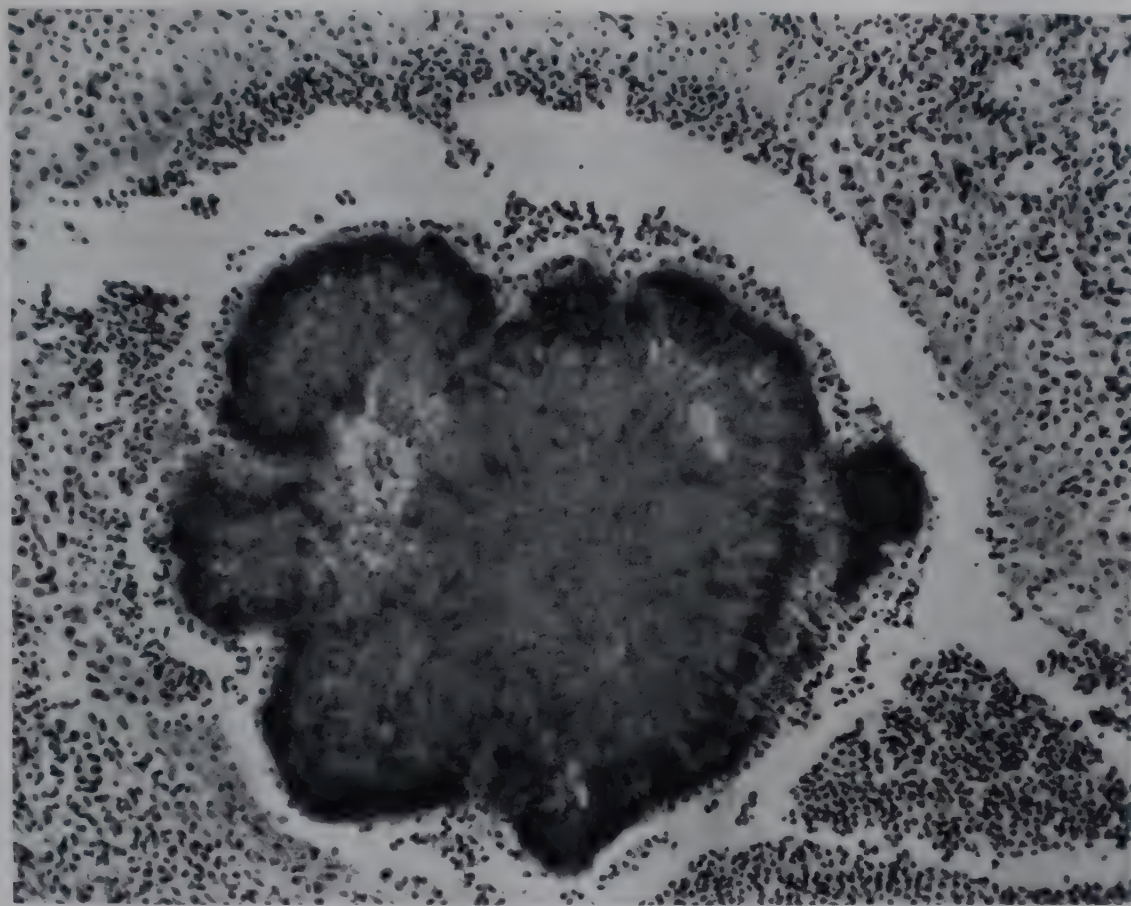


Fig. 218. Actinomycotic granule in an abscess of the liver.

organ affected, the degree of chronicity, and the presence or absence of secondary infection.

Actinomycosis in Animals. The classical example of actinomycosis is "lumpy jaw" of cattle, in which the organism enters the lower jaw through a wound in the mouth produced by chewing straw or grain, and a large abscess with partial destruction of the mandible results.

Special Types. Erythrasma is caused by *Actinomyces minutissimus*, and there is a superficial inflammation with macular scaly lesions in the axilla, groin, intergluteal cleft, and other intertriginous regions. Nocardiosis, also known as streptothricosis, is caused by aerobic strains of actinomyces.

Blastomycosis

The term "blastomycosis" has over the years had different meanings. The disease

therefore these have been called "paracoccidioidal granulomas."

American Blastomycosis. This disease is frequently termed "Gilchrist's disease." There are two general types: cutaneous and systemic.

Cutaneous Blastomycosis. The initial lesion is a nodule in the subcutaneous tissue that soon softens and ulcerates. This initial lesion extends rapidly by the formation of numerous small nodules about the periphery and incorporation into the original nodule or abscess. Eventually large, irregularly outlined, firm, papillomatous or ulcerating plaques are produced on any part of the body, but more especially on the extremities or on the skin of the head and neck. Microscopically, hyperplasia of the epithelium and numerous small abscesses in the epidermis are seen. The rete pegs extend deeply into the dermis and anastomose with one another. The basal layer is

in all instances intact. Within the connective tissue enclosed by the anastomosing rete pegs abscesses form. In the surrounding tissue there is moderate infiltration, especially perivascularly, with lymphocytes, polymorphonuclear leukocytes, and plasma cells. About some of the abscesses there are epithelioid cells and occasional giant cells (Fig. 219).

Systemic Blastomycosis. Systemic blastomycosis may occur with or without cutaneous blastomycosis. The lung is the organ most frequently affected. Throughout the parenchyma there is a diffuse and focal consolida-

tion or on Sabouraud's medium. Final identification of genus and species depends on certain cultural and biochemical characteristics of the organism. Complement-binding bodies are found in the blood of those with severe infections, and in many instances a hypersensitivity of the skin to a filtrate of a culture can be demonstrated. The organisms occur in nature, but the exact mode of transmission is not known.

Clinicopathologic Correlation. Cutaneous blastomycosis, although a serious disease, responds to treatment, and the mortality is low.

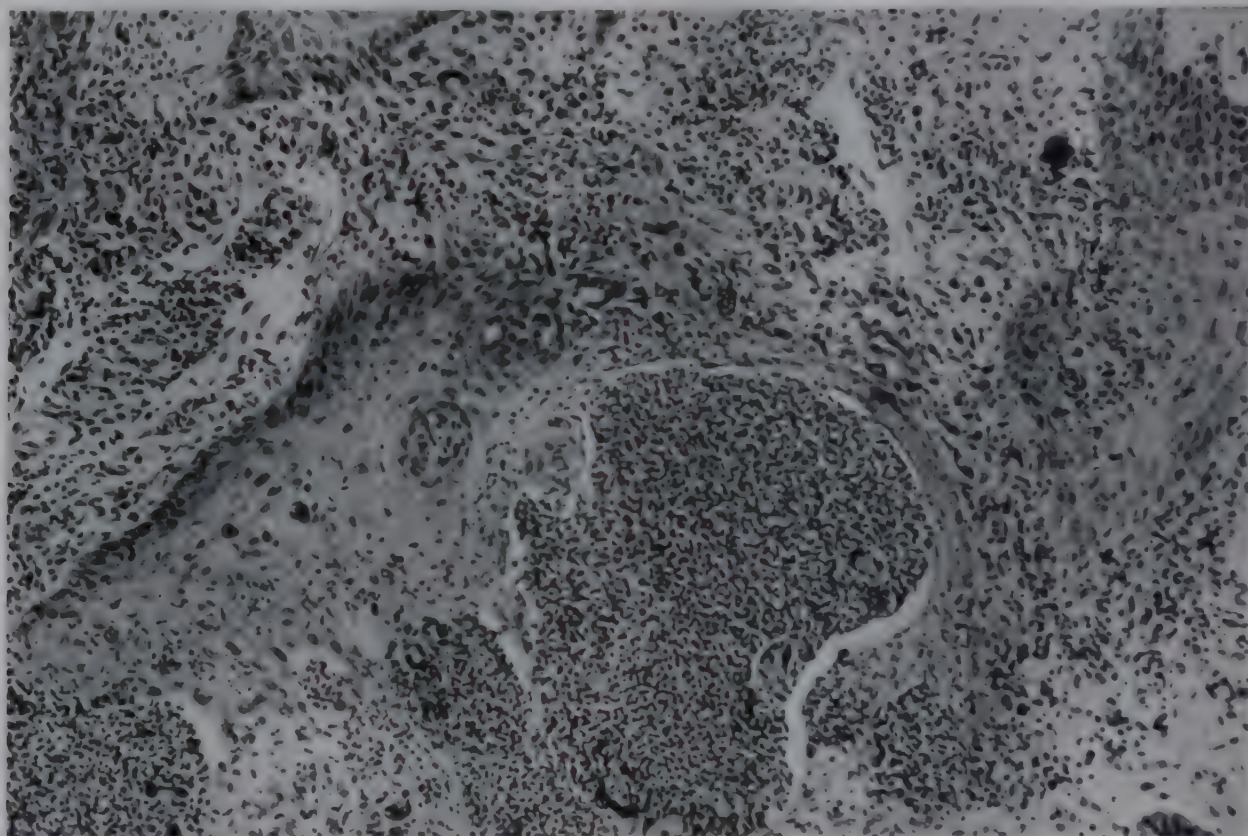


Fig. 219. Cutaneous blastomycosis. Note the acanthosis and formation of abscesses. (Photograph by courtesy of Dr. Morris Moore.)

tion, representing confluence of numerous small and large, yellow, moderately well outlined nodules, similar to the tubercle. Cavities form, but they rarely exceed 1 cm. in diameter. Microscopically the lesions are similar to the tubercle, except that there is less caseation in the centers of the nodules, and the polymorphonuclear leukocyte is present in moderate numbers (Baker). Similar lesions have been reported in the heart, spleen, kidneys, liver, adrenals, and skeletal muscle. Occasionally a suppurative type of arthritis or osteomyelitis is caused by blastomycetes. There is a basilar meningitis, or multiple blastomycotic nodules in the brain, in about one-third of cases.

Causal Agent. The organisms can be identified in the tissues or in the pus from many of the lesions, or can be grown on blood agar

Systemic blastomycosis has a mortality approaching 100 per cent. The signs and symptoms depend upon the presence of an infecting agent in the body and local tissue destruction. Thus in pulmonary blastomycosis the signs and symptoms would be similar to, if not identical with, those of pulmonary tuberculosis.

Paracoccidioidal Granuloma. South American Blastomycosis. There are two forms of this disease, a localized and a generalized. The localized form is found most frequently in the buccal mucosa. The appearance of the lesions is similar to that in North American blastomycosis (Moore).

Cryptococcosis

The original descriptions of what is now known as cryptococcosis were given under

the title of "Infections Caused by *Torula*," and many persons still designate the organism as "*Torula histolytica*." The accepted systematic name is "*Cryptococcus hominis*."

Pathologic Anatomy. Lesions are most frequently found in the central nervous system, but are occasionally seen in the lung, in the skin (Wile), and as a generalized infection (Longmire and Goodwin). The degree of reaction of the tissues to the presence of the cryptococcus is variable. The typical lesion is

for the isolation of the organism is the intraperitoneal injection of mice. Mycelia are never formed in tissue.

Transmission. Numerous species of cryptococcus are found in nature, but the exact mode of transmission to man is not known. It seems probable that the gastro-intestinal and the respiratory tracts are the portals of entry, and that the organism enters the meninges through the lymphatic drainage of the nose and pharynx.

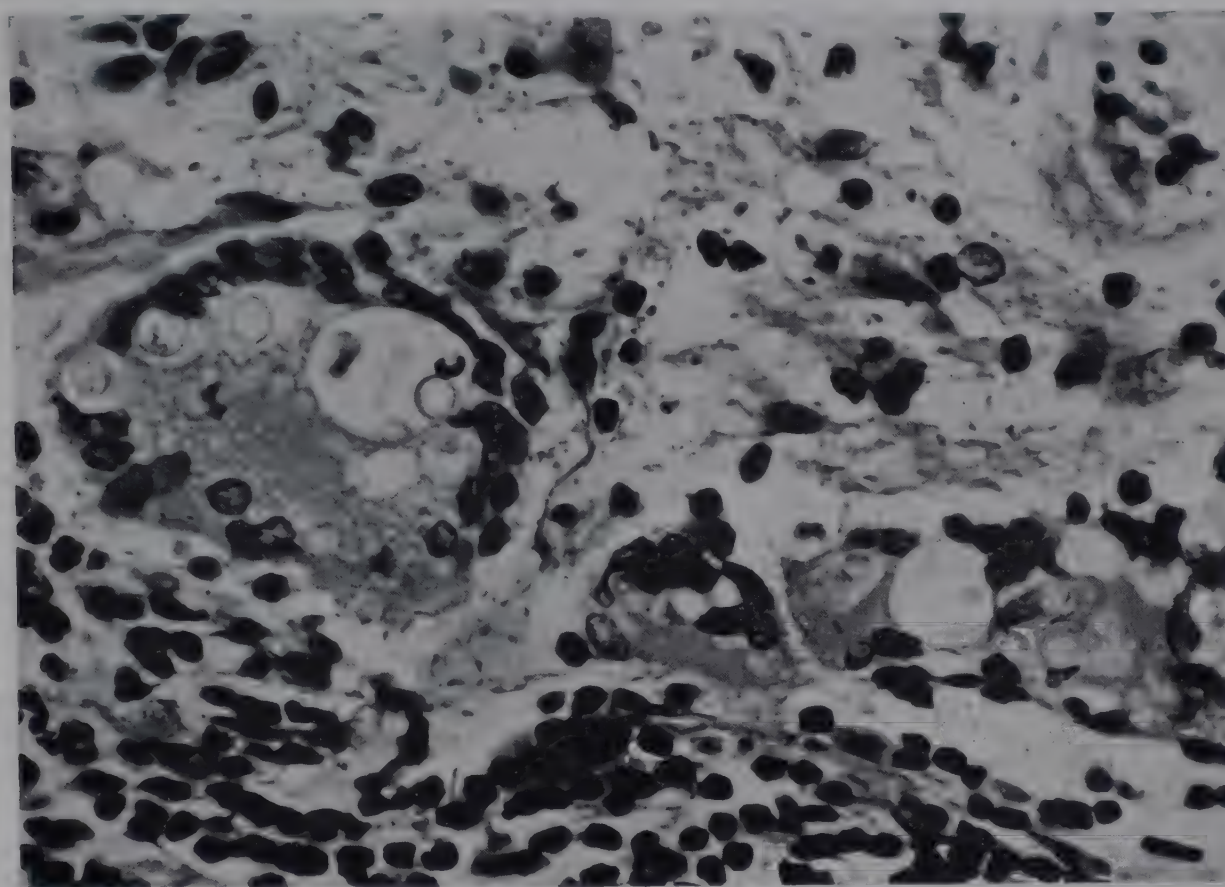


Fig. 220. *Cryptococcus hominis* in the tissue about a cyst of the brain. Giant cells have formed about the organisms.

in the form of a cystic cavity within the substance of a solid viscus, filled with a gelatinous fluid. Typical, double-walled or spined organisms are in the fluid or in giant cells (Fig. 220). In the surrounding tissue there may or may not be a cellular reaction. The dominant cell is the mononuclear cell, but some lymphocytes and polymorphonuclear leukocytes may be present. There is little necrosis in the surrounding tissue, and it would appear that the cyst is formed by the secretion of the gelatinous fluid by the organism and pressure on the surrounding tissue. Cysts are found in the meninges and in the brain substance (Reeves, Butt, and Hammack). In the lung the affected focus is consolidated, and on section a mass of viscid fluid can be scraped from the surface.

Causal Agent. The most satisfactory method

Clinicopathologic Correlation. Clinical changes may result from infection or from destruction of parts of the central nervous system. There are few systemic symptoms. Recovery is rare, if it ever occurs (Longmire and Goodwin).

Coccidioidomycosis

During the first century of occupation of California by the white man, two distinct disease entities were established and recognized, valley or desert fever and coccidioidal granuloma. More recent investigation has shown that they are caused by the same fungus, *Coccidioides immitis*, and represent a first infection and reinfection type of response respectively (Dickson).

Primary Coccidioidomycosis. This is the

designation now given to the condition known in lay terms as "valley fever."

Pathologic Anatomy. The pathologic changes have not been described, since it is invariably a mild condition and deaths have not been observed. In roentgenograms of the chest there are dense shadows in the hilar

with coccidioides. The nodules are composed of caseous and partially calcified material, and the organism can be demonstrated within the nodule (Cox and Smith). This finding is of importance in evaluating the significance of calcified nodules, since it indicates that another disease can reproduce perfectly the

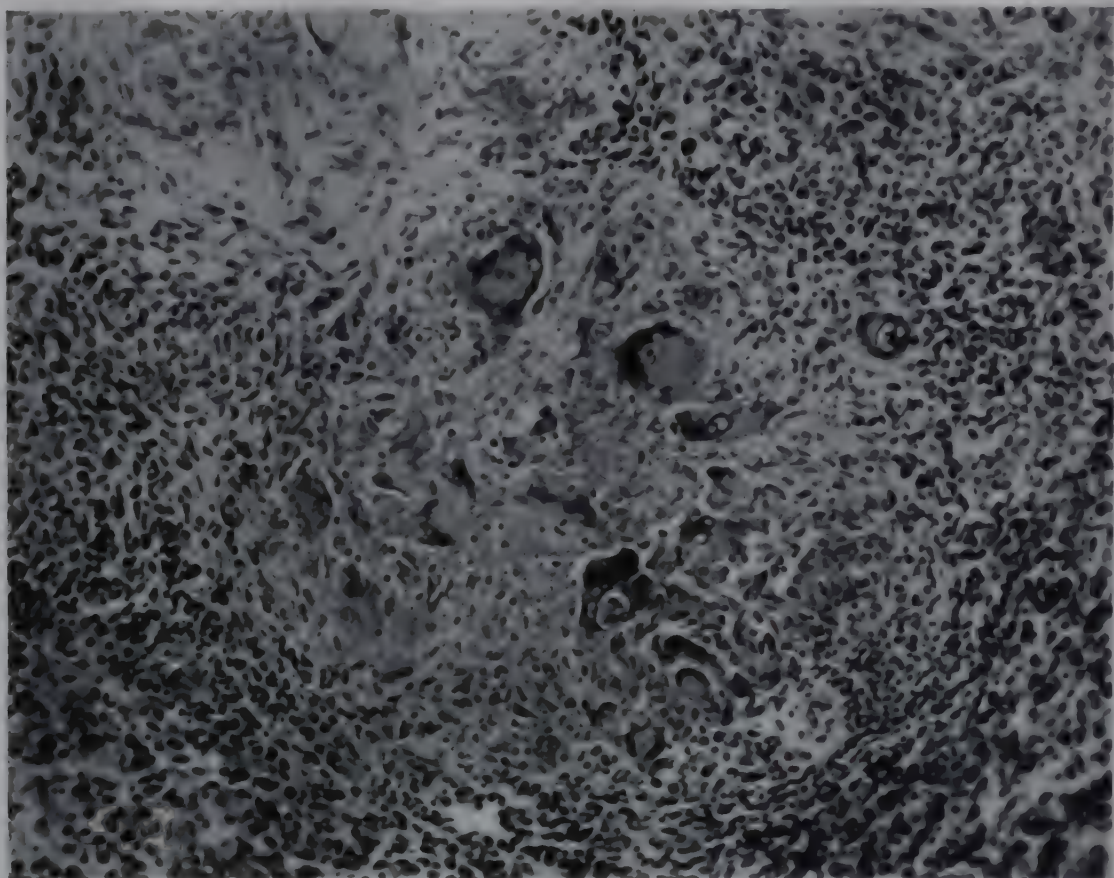


Fig. 221. Coccidioidal granuloma in the lung. (Tissue by courtesy of Dr. James McNaught.)

region, indicating an enlargement of the lymph nodes. Radiating from the hilum there are irregular densities in the parenchyma, interpreted as infiltrations in the peritruncal tissue, bronchitis, and pneumonic consolidation. There is a moderate productive cough, and

anatomic changes of tuberculosis (Aronson, Saylor, and Parr).

Coccidioidin. Within one to two weeks after the onset of valley fever, the skin becomes sensitive to a filtered broth culture of the organism. The extent of the infection in the

TABLE 23. REACTION TO COCCIDIOIDIN

Place Where Study Was Made	Type of Persons	Number of Persons	Percentage Positive
Kern County, Cal.	school children	3307	58.2
Gila Crossing, Ariz.	school children	141	90.1
Ann Arbor, Mich.	university students	70	0
San Francisco	hospital patients	260	4.23
Philadelphia	school children	15	0

the organisms are readily identified in smears of the sputum or by culture. So far as can be determined, recovery is complete (Winn). Precise pathologic studies have shown, however, that calcified nodules in the lung and in the draining lymph nodes of persons in California may result from a previous infection

San Joaquin Valley is shown by the fact that 17 per cent of persons who have lived in the valley less than one year are sensitive, while 77 per cent of those there for over ten years have a positive coccidioidin test. The specificity of the reaction is well demonstrated in Table 23 (Farness). So far as can be deter-

mined, this sensitivity remains for many years, if not for life.

Progressive Coccidioidal Granuloma. Two types are generally recognized, cutaneous and pulmonary, although in both there may be systemic lesions.

Pathologic Anatomy. The general pathologic changes are similar to those of tuberculosis. Small nodules, 1 to 2 mm. in diameter, are formed within the tissue. Occasionally these nodules coalesce, undergo necrosis, and form a cavity, but the cavities are rarely over a centimeter in diameter, and there is little fibrous tissue reaction about them (Winn). The nodules are composed of a dense infiltration with polymorphonuclear leukocytes and monocytes, with at times necrosis of the center. There is little proliferation of fibrous tissue about the nodules and no definite delineation of epithelioid cells and giant cells, such as are seen in the typical tubercle. There are, however, giant cells within which the organisms are found (Ophuls). Examples of coccidioidal infection of the meninges and of the peritoneum have been described. The organisms are readily recoverable on inoculation into guinea pigs, rats, and mice, or cultivation on special media.

Transmission. Endemic foci of coccidioidomycosis have been recognized in the San Joaquin Valley of California, in certain parts of Arizona and Texas, and in one local area of Argentina. There is definite evidence that the disease is not transmitted from man to man, but that the chlamydospores in the dry soil and in dust are the source of human infection. Rodents, dogs, sheep, and cattle may serve as animal reservoirs (Stiles and Davis).

Clinicopathologic Correlation. The incubation period of valley fever is seven to twenty-one days, and a second attack is rare. Clinical changes in coccidioidal granuloma of the lung are similar to those of pulmonary tuberculosis. The mortality is about 50 per cent. In experimental animals the inoculation intratracheally of a very few spores will reproduce valley fever, but an overwhelming inoculation gives rise to coccidioidal granuloma.

✓ *Rhinosporidiosis*

This rare condition is observed as soft polypoid masses within the nasal cavity. The characteristic organisms are seen within the

tissues, each about 100 microns in diameter, surrounded by doubly contorted chitinous-appearing capsules. In the center there is a nucleus, and the cytoplasm contains numerous nutrient granules. The capsule ruptures at one point, and the spores are discharged into the tissues. Between the organisms there is a relatively dense fibrous tissue, infiltrated with lymphocytes, plasma cells, and foreign body giant cells. The organism is known as “*Rhinosporidium seeberi*” or “*Rhinosporidium kienealyi*.” There are three foci of this disease in the world: India, Argentina, and the United States.

Maduromycosis

Pathologic Anatomy. The well-developed lesion of maduromycosis, called also “mycetoma” or “Madura foot,” is usually on the foot, but occasionally is found on the hand, on other parts of the extremities, and rarely on the trunk. The part affected is enlarged, firm, irregular in outline, and often deformed; and opening onto the skin surface are numerous sinus tracts from which a thick yellow fluid exudes. On section the sinus tracts intercommunicate and penetrate deeply into the tissues. Between the sinuses is firm fibrous tissue with numerous small yellow nodules composed of caseous material or thick yellow pus. The skin between the sinuses is deformed, dark red, and extensively scarred. The walls of the sinus tracts are lined with granulation tissue, and beneath this is a dense mass of fibrous tissue with slight infiltration with lymphocytes and thickening of the blood vessels. Within the granulation tissue are lymphocytes and occasional epithelioid cells and giant cells. The pus within the sinuses and within the small yellow nodules contains numerous polymorphonuclear leukocytes and colonies of the organism (Thompson).

Causal Agent. *Madurella* is readily identified in the pus as small yellow, brown, or black granules. It is not pathogenic for animals, but can be cultured (Gammel). Agricultural workers and persons who wear no shoes apparently pick up the organism from the soil through a small traumatic lesion.

Clinicopathologic Correlation. The enlargement and the deformity of the part as the result of fibrous tissue proliferation and the constant draining of pus cause the foot or hand

to become useless. Secondary infection occasionally enters through the sinus tracts and may modify the clinical picture.

Histoplasmosis

After the original description by Darling in 1905 histoplasmosis was regarded as a rare, uniformly fatal disease until the 1940's when two types of studies focused attention on it. First, several laboratories reported multiple cases (Parsons and Zarafonitis; Beamer, Smith, and Barnett); and, second, evidence

and in the mucosa of hollow viscera ulcerate.

Any tissue or organ may be involved but lesions are more common in skin, buccal cavity and nose (Weed and Parkhill), larynx, lymph nodes, lungs, liver, spleen, intestine and adrenal. Rare lesions include vegetative endocarditis (Beamer, Reinhard, and Goodof) and arthritis (Rey and Large).

There is a primary pulmonary type in which a caseous nodule in the lung and caseation of the tracheobronchial nodes exactly duplicate the first infection lesion of tuberculosis (Schulz).

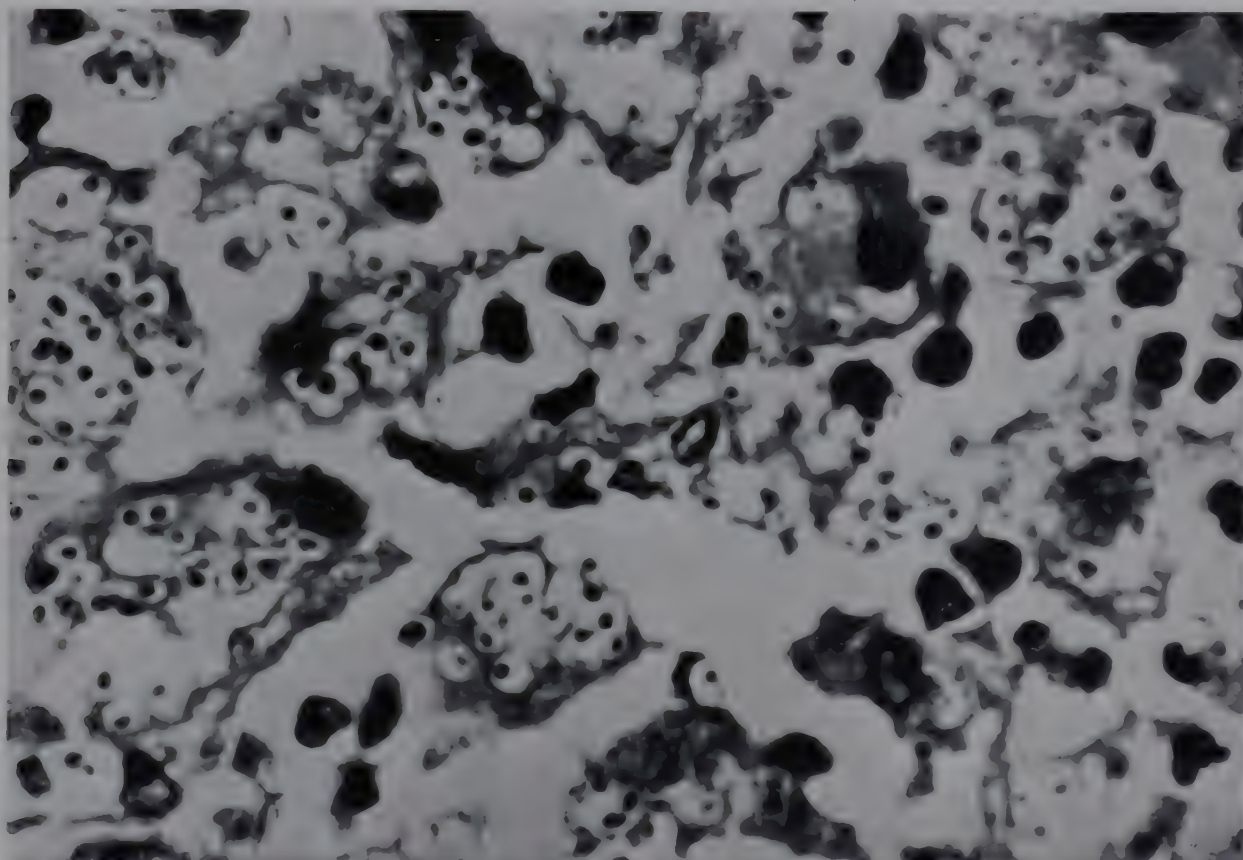


Fig. 222. Histoplasmosis. Note organisms in large mononuclear cells. (Photograph by courtesy of Dr. Morris Moore.)

accumulated that pulmonary calcification may result from nonfatal infections (Bunnell and Furcolow).

Pathologic Anatomy. The essential pathologic change in histoplasmosis is parasitism of the cells of the reticulo-endothelial system by organisms. Typically, in an acute lesion, mononuclear cells are enlarged and the cytoplasm filled with small basophilic bodies 1 to 3 microns in diameter surrounded by a clear halo (capsule) with an overall diameter of 3 to 5 microns (Fig. 222). Characteristically the parasitized cells are collected together in small granulomas, but they may be distributed diffusely.

In larger granulomas there is central necrosis of a caseous type similar or identical with that of tuberculosis. Lesions of the skin

Causal Agent. *Histoplasma capsulatum* is a fungus which occurs in the tissue in a yeast form and grows in culture media in hyphae. For direct isolation, media enriched with blood or Sabouraud's medium should be used. A filtrate of cultures is available for a skin test which is useful in diagnosis.

Transmission. The exact mode of transmission is unknown. The disease has been observed in dogs (Callahan). The high incidence of lesions of the nose and mouth, lung, and gastro-intestinal tract (Henderson, Pinkerton, and Moore) suggest these as portals of entry.

Clinicopathologic Correlation. Clinically the disease histoplasmosis may assume an acute disseminated form, a chronic disseminated form, and a nonfatal pulmonary form.

In all there are the signs of an infection, the severity depending on the acuteness. The diagnosis may be established by biopsy, by sternal marrow aspiration, and rarely by identification of the organism in cells of the peripheral blood. In chronic forms the granulomas are fibrotic and organisms may be absent.

Nonfatal Disease and Pulmonary Calcification. In some parts of the United States there is a significant number of individuals with multiple calcified nodules in the lung, a negative tuberculin test, and a positive histoplasmin test (Palmer). Further, patients have been observed with a pulmonary infection in whom histoplasma was isolated from the sputum, and who subsequently and sequentially developed calcified nodules in the lungs (Bunnell and Furcolow). It therefore appears that histoplasmosis is one cause of pulmonary calcification along with tuberculosis and coccidioidomycosis.

Aspergillosis

The organism *Aspergillus* is of low virulence and requires destruction of tissue from some other cause before it can excite an inflammatory reaction. The disease is acquired by man from contact with grain. In the lung the bronchi are filled with pus and the mucosa is swollen and red. Throughout the parenchyma there are numerous small white nodules. In the pleura there is a purulent inflammation, or in more chronic cases fibrous obliteration of the pleural cavity. There is an acute inflammation within the bronchi and in nodular form in the lung, characterized by an infiltration of polymorphonuclear leukocytes. Mycelia of the organism are readily demonstrated (Schneider).

Aural Aspergillosis. Infection of the external and middle ear with *aspergillus* is common in certain parts of the world, especially in China, where it has been given the special name "Hong Kong ear." Within the external auditory canal a thick, firm, greenish cerumen forms (Felderman).

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LIV

Diseases Caused by Protozoa

Protozoa are animals composed of a single cell in which are performed all of the functions of life. A few are pathogenic for man, and are the cause of many of the important so-called "tropical" diseases. A few are parasitic in the gastro-intestinal tract of man, but apparently do not produce any significant disease.

Incidence. It is not possible to compare the data on the frequency of infection in different

at the University of Pennsylvania. A state of parasitism is sometimes the equivalent of the carrier state in bacterial diseases.

Transmission. There are three general sources of infection with the protozoan parasites: contaminated food, insect vectors, and direct contact with a diseased person. Most of the intestinal protozoan parasites are transmitted by contaminated food. Malaria and leishmaniasis are directly dependent on bio-

TABLE 24. FREQUENCY OF INFESTATION WITH PROTOZOA

Protozoa	4270 White Clinic Patients in New Orleans (Faust & Headlee)	20,237 Persons in Rural Tennessee (Meleney, Bishop, & Leathers)	700 Fresh- men at the University of Pennsyl- vania (Wenrich, Stabler, & Arnett)	1003 Persons in Puerto Rico (Faust, Hoffman, Jones, & Janer)	3146 Persons in Great Britain	13,617 Patients at the Peiping Union Medical College Hospital (Faust)
Endamoeba histolytica . . .	8.4	11.5	4.1	14.5	3.4	20.3
Endamoeba coli	12.4	31.6	13.9	34.2	18.1	16.6
Endolimax nana	19.3	13.5	11.3	16.3	4.6	28
Iodamoeba bütschlii	0.9	4.2	1.3	3.5	0.25	6.6
Giardia lamblia	16.5	9.5	7.9	14.3	9.3	6.7
Chilomastix mesnili	0.4	3.2	0.7	0.7	2.9	4.7
Trichomonas hominis	0.9	0	0	3.5
Balantidium coli	0.02	0	0.2

parts of the world because of differences in population, in the technique of examination, and in the evaluation of results, but the percentages given in Table 24 will serve as a general index. It is clear that infection is common in all types of population and in all parts of the world, but that it is greater in tropical and semitropical countries than in the North Temperate Zone. It is also clear that infection with a protozoan parasite does not necessarily mean disease—witness the infection with Endamoeba histolytica in freshmen

logical transmission by an insect. Other insects may on occasion serve as mechanical vectors for the intestinal parasites. Contact infection between persons is occasionally observed in amebiasis and in leishmaniasis. Some of the parasites are strictly confined to man, while others are carried by animals, either with or without manifest disease. For example, Balantidium coli is a parasite common to pigs and to man, and kala-azar is caused by the same parasite which is responsible for lesions of the skin in dogs.

Endamebiasis

Pathologic Anatomy. *Endamoeba histolytica* produces characteristic and typical pathologic changes in the colon, liver, and lungs. In the colon the gross lesions vary from a minute, raised, hyperemic papule to large confluent ulcers, and may best be described on a pathogenetic basis. The cysts of the amebas are swallowed with contaminated food or water and after passage through the stomach, excyst in the jejunum and ileum. On reaching the colon they attach to the surface

the submucosa, adjacent ulcers may come into contact with one another, undermining the mucosa—a pathognomonic feature of amebic dysentery not found in any other type of ulcerative colitis (Fig. 224). With the appearance of deep ulcers there is frequently secondary bacterial infection. This is associated with cellular infiltration with polymorphonuclear leukocytes and lymphocytes (Mackie; Meleney). Lesions are most common about the ileocecal valve and in the rectum.

Amebic Hepatitis and Abscess. Amebas enter the portal circulation and lodge in the

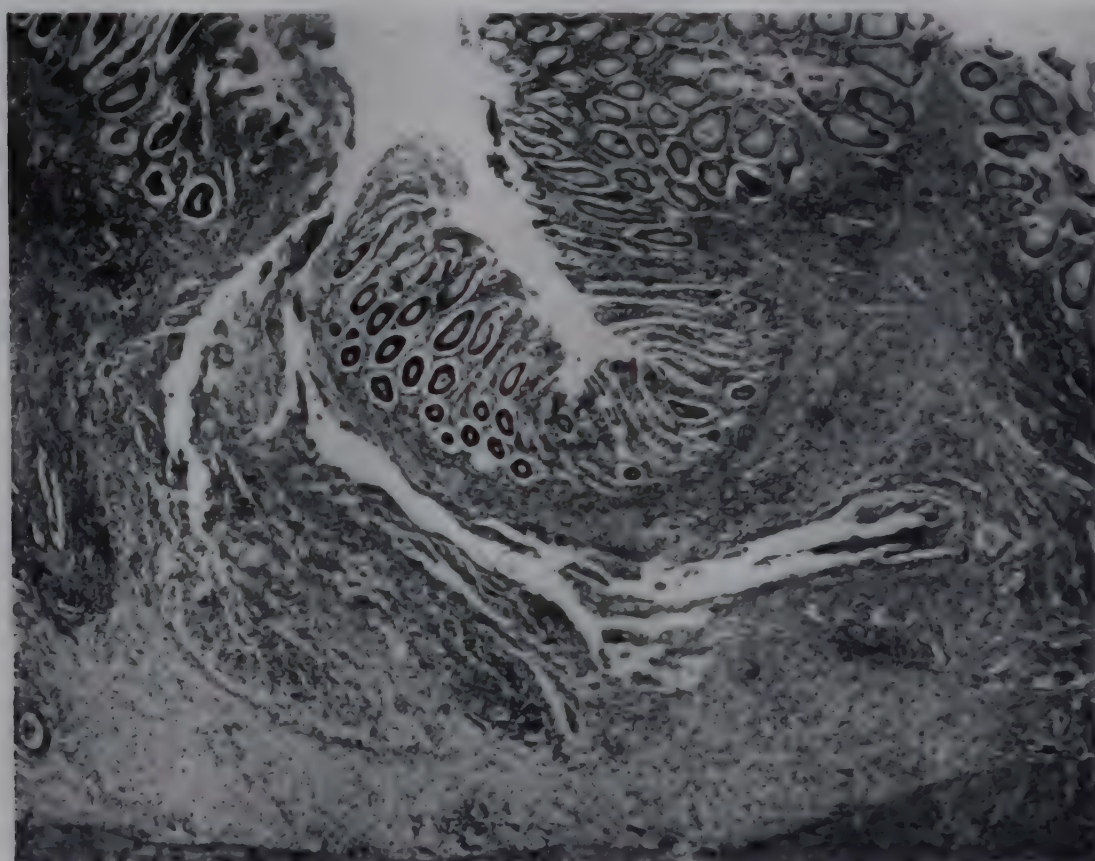


Fig. 223. Flask-shaped ulcer in endamebiasis. Note the small ulceration in the mucosa and the spread through the submucosa.

of the mucosa or penetrate beneath the epithelial cells into the connective tissue. Here they multiply and penetrate as far as the muscularis mucosa. There are edema and hyperemia, but very little cellular infiltration. Lytic substances are produced by the organism, which brings about necrosis and solution of the tissues in contact with them. At this stage there is a small ulcer involving only the mucosa (Faust).

The organisms gain entrance to the lymphatics and penetrate through the muscularis mucosa into the submucosa. Here they spread out in all directions and produce in the submucosa larger areas of necrosis than those in the mucosa—the flask-shaped ulcers of amebic dysentery (Fig. 223). In the necrosis of

liver. Undoubtedly most are rapidly destroyed, probably by the mechanism demonstrable in vitro of the amebastatic or amebacidal action of liver (Faust). In some patients there is a diffuse hepatitis manifested by jaundice and other signs and symptoms (Sodeman and Lewis). In others abscess of the liver develops. The abscess may be single or multiple, and is more frequently in the right lobe than in the left. The smallest lesions are spherical foci of liquefaction, which microscopically show large numbers of amebas with little cellular infiltration. The larger abscesses are filled with a thick purulent or sanguinopurulent exudate. The wall is lined by an inner, shaggy network of fibrin and an outer layer of fibrous tissue. In the fibrous tissue and in

the fibrin there is an infiltration with mononuclear cells. In the surrounding parenchyma there are compression atrophy, fatty degeneration and an increase of fibrous tissue in the portal canals. Occasionally there are demonstrable thrombi in the radicles of the portal vein. Secondary bacterial infection is present in about 15 per cent of cases (Palmer, Ochsen, and DeBakey; Councilman and Lafleur).

Extension through Diaphragm. In about 15 per cent of persons with an amebic abscess of the liver there is extension through the diaphragm, and involvement of the pleura or lung or both (Fig. 226). In some there is actual perforation of the diaphragm, and in others the amebas migrate through the tissues of the diaphragm. The pus in the pleura or



Fig. 224. Amebic ulcers of cecum. Note the undermining and the small bridge of intact mucosa between two adjacent ulcers.

in an abscess of the lung is reddish brown and thick. Erosion of the surface of the lung, with the formation of bronchopleural fistulas, is not uncommon. Less commonly there is extension to the pericardium (Kern).

A rare example of leukorrhea or bloody vaginal discharge is caused by ulcerative amebiasis of the vagina and cervix (Weinstein and Weed).

Causal Agent. *Endamoeba histolytica* in

the tissues is from 20 to 25 microns in diameter and contains a single darkly staining nucleus with a prominent nuclear membrane. In the cystic stage, found in the stools, there are two or four nuclei, and this stage varies from 7 to 14 microns in diameter. When the cyst is reintroduced into the gastro-intestinal

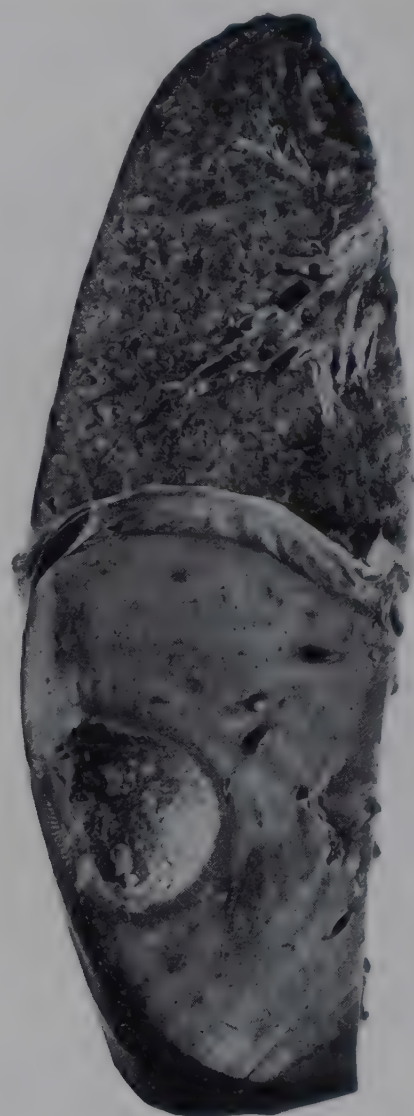


Fig. 225. Amebic abscess of liver, with subphrenic abscess and amebic inflammation of lung.

tract, the nuclei multiply so that there are eight, and the cytoplasm then divides and produces eight trophozoites, which invade the tissues. The organism can be grown on special culture media, but dies out in pure culture. In about 70 per cent of persons with amebas in the stool a positive complement-fixation test can be secured. The antigen is made from the culture strains. Colonic lesions similar to those in man can be produced experimentally in kittens (Meleney and Frye). The presence of pathogenic bacteria or mechanical trauma to the mucosa, as well as the presence of amebas, may be necessary for the production of the disease (Nauss and Rappaport).

Transmission. Endamebiasis is transmitted from man to man by contaminated food and water. Flies may serve as mechanical vectors.

In the Orient where human excreta are used for fertilizer the incidence of the infection is high. In the United States there are few actual infections, but a not inconsiderable number of persons are carriers; for example, in New Orleans in 200 autopsies on persons killed in automobile accidents, 13 were found to harbor *Endamoeba histolytica* and to have demonstrable lesions of the wall of the intestine.

Incidence. The disease is worldwide in distribution, and is most common in man between the ages of twenty and thirty years. It is rare in children under five years.

There are three forms: (1) cutaneous leishmaniasis—Oriental sore; (2) mucocutaneous leishmaniasis—American leishmaniasis; and (3) visceral leishmaniasis—kala-azar.

Cutaneous Leishmaniasis. *Pathologic Anatomy.* The initial lesion is a papule on the exposed part of the body, usually the face, neck, hands, or feet. The papule enlarges and ulcerates to form a sharply punched-out ulcer, with a raised, indurated border. The base is formed of granulation tissue, covered by a heavy brown crust and a thin serous exudate. With healing, a firm, depressed, gray scar re-

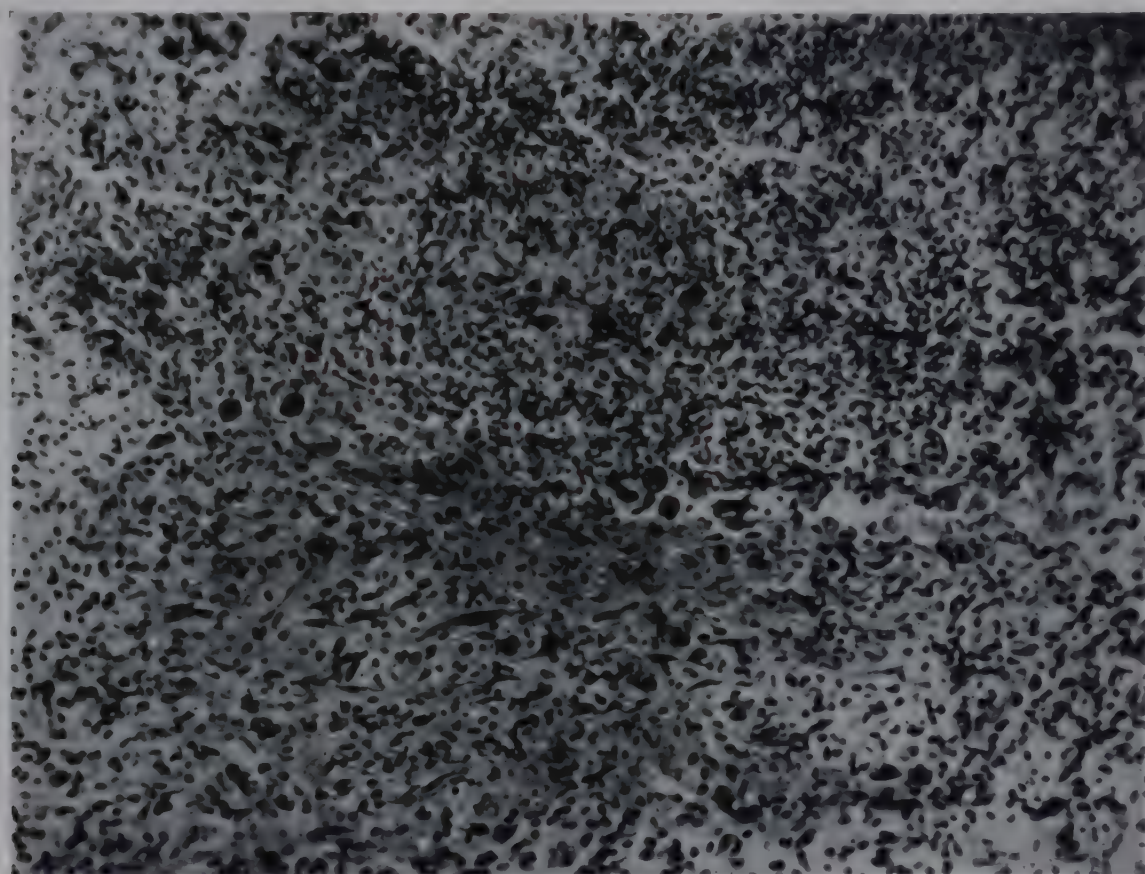


Fig. 226. Wall of amebic abscess of liver. Note the larger endamebas at the junction of the necrotic and viable tissue.

Clinicopathologic Correlation. The presence of ulcers in the intestine, most common in the cecum and ascending colon, is responsible for the principal sign, a dysentery characterized by frequent bloody, mucoid stools. The abscesses of the liver give rise to the usual picture of a pyelephlebitis, i.e., fever and chill, and to enlargement of the liver with jaundice. The abscesses of the lung and the empyema produce cough and pain in the chest. Amebas may be found in the sputum. The mortality of the disease as a whole averages about 40 per cent. Ulceration and gangrene of the skin are rare complications (Wyatt and Buchholz).

Leishmaniasis

Leishmaniasis includes those diseases caused by protozoa of the genus *Leishmania*.

The earliest microscopic lesion is a focal accumulation of mononuclear cells filled with parasites in the dermis. This focus increases in size, and there follows an infiltration with lymphocytes and plasma cells. Infiltration with polymorphonuclear leukocytes is usually an indication of secondary infection. The epidermis is stimulated to growth, and there are numerous retes extending down into the dermis, simulating the picture of epidermoid carcinoma. With central necrosis there is ulceration onto the surface, and further proliferation of the epithelium at the edges. Healing is accomplished by growth of granulation tissue and filling of the ulcer. There are no changes in the viscera in cutaneous leishmaniasis (Ball and Ryan).

Causal Agent. The causal agent of cutane-

ous leishmaniasis is *Leishmania tropica*. It can be demonstrated in the exudate during early stages of the ulcer, but later aspiration of the tissues or biopsy may be necessary to establish the diagnosis. Morphologically, *Leishmania tropica* is identical with *Leishmania donovani*. It may be cultured in N.N.N. medium. Monkeys, dogs, rats, mice, and guinea pigs are susceptible. The most common method of *transmission* is probably through the bite of the sandfly, *Phlebotomus papatasi* (Southwell and Kirshner). A similar disease of dogs may serve as a reservoir. Contact infection from other human beings is believed to occur. One attack confers lasting immunity.

Incidence. Most persons in endemic areas are infected at an early period of life. These areas are the Near East, about the Mediterranean, and in northwest India. In each focus a special name is used: Oriental sore, tropical ulcer, Bagdad button, Aleppo boil, and Lahore sore. In the United States, where all cases are imported, the condition is usually seen in adults (Dwork).

Clinicopathologic Correlation. The incubation period varies from a few days to several months. There are few if any systemic symptoms or signs. Multiple lesions from auto-inoculation occur. Death from cutaneous leishmaniasis is rare, but secondary bacterial infection may be fatal. Healing is usually complete in one year.

Mucocutaneous Leishmaniasis. Pathologic Anatomy. The gross and microscopic appearances of the lesions of the skin are identical with those in cutaneous leishmaniasis. In about 20 per cent of patients there are in addition lesions of the mucous membranes. The anterior third of the nasal septum is most frequently affected, followed by the mucous membrane of the pharynx, larynx, and buccal cavity. The mucous membrane is red, elevated, firm, and granular. There is infiltration with monocytes, lymphocytes, and plasma cells. Proliferation of epithelium and of granulation tissue may form a negative type. Superficial ulceration is the rule, and healing leaves a large scar. Lesions in the nasal septum may result in extensive destruction of tissue. Protozoa are present in large numbers in the mononuclear cells. There are no changes in the viscera (Fox).

Causal Agent. *Leishmania braziliensis* is

morphologically identical with *Leishmania donovani*. The parasite is readily demonstrated in material obtained by puncture of the edge of the ulcer, or in scrapings of the mucous membrane. It may be cultured on N.N.N. medium. The method of transmission is unknown, but the sandfly, *Phlebotomus intermedius*, may be the insect vector. Some consider *Leishmania braziliensis* as a variety



Fig. 227. The opened abdomen in a case of kala-azar, showing the extreme enlargement of the spleen and moderate enlargement of the liver. (Photograph by courtesy of Prof. C. H. Hu.)

of *Leishmania tropica*, but there are definite serologic differences.

Incidence and Distribution. The condition is most common in young adult men, and endemic areas are found throughout Central and South America. Rural workers on chicle and rubber plantations are especially affected. Other names for the condition are American leishmaniasis, espundia, uta, and forest yaws.

Clinicopathologic Correlation. The length of the incubation period is unknown. Cutaneous lesions heal in a few months to two years.

Lesions of the mucous membranes appear before or weeks after the cutaneous ulcers have healed, and persist for years. Death usually results from the complication of septicemia or from bronchopneumonia.

Kala-Azar. *Pathologic Anatomy.* The basic pathologic change is a symbiotic parasitism of large mononuclear cells (clasmatocyte of Sabin) and multiplication of these cells in all tissues of the body. The increase in the number of cells is enormous and leads to enlargement of the viscera. There is an associated congestion, so that the individual organs may be described as enlarged, red, and moderately

numbers of the Leishman-Donovan bodies (Meleney).

Causal Agent. The causal agent of kala-azar was first observed by Leishman at Dumdum, India, in 1900 (hence the name, "Dumdum fever"). Donovan in 1903 described similar organisms in material obtained by splenic puncture from a living patient with kala-azar. In the endothelial cells of man and other mammals *Leishmania donovani* is a small, round or oval body, 2 to 3 microns in longest diameter. The cytoplasm is palely basophilic, enclosing a relatively large acidophilic nucleus. In the cytoplasm at right angles

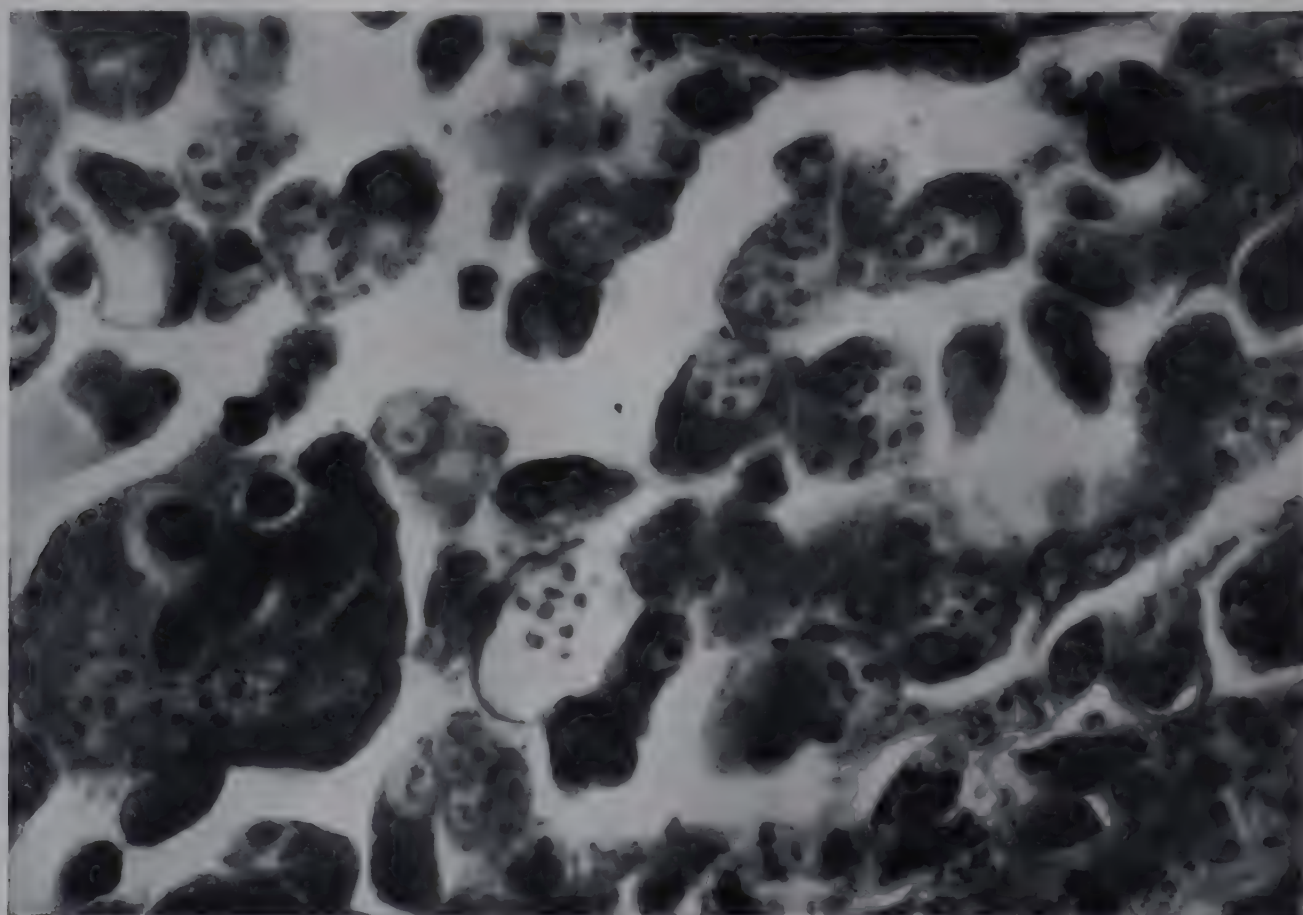


Fig. 228. Leishman-Donovan bodies in experimental leishmaniasis of the hamster. (Armed Forces Institute of Pathology, Neg. No. 45067.)

firm. The spleen is most frequently affected, and may weigh up to 3000 gm. (Fig. 227). The capsule is slightly thickened. The cut surface is dark red or purple. The malpighian bodies are conspicuous. The liver is next most frequently affected. It is enlarged, and the parenchyma is grayish yellow and moderately firm. The bone marrow is soft and red. The lymph nodes are usually enlarged, soft and gray. In addition to these four hematopoietic organs, the intestine, testes, lungs, adrenals, pancreas, skin, kidneys, and meninges are likely to show similar changes, in the order named. There is in all organs multiplication of the endothelial cells and blocking of the capillaries. All of these cells contain enormous

to the nucleus there is an acidophilic, rod-shaped body called the "kinetoplast." On precise analysis the kinetoplast is found to consist of a rodlike, parabasal body, and a dotlike blepharoplast. A delicate, acidophilic filament may be seen extending from the kinetoplast to the cell wall—the axoneme. Slender, fusiform organisms may also be observed.

Leishman-Donovan bodies may be cultured on N.N.N. medium, and under these conditions show the other half of the life cycle—a flagellate or leptomonad form. The organism is pear-shaped or long spindle-shaped. The nucleus and kinetoplast are similar to those of the leishmanial form in mammalian tissue. From the kinetoplast of flagellum, 15

to 25 microns in length, extends into the surrounding medium. In the gastro-intestinal tract of insects similar flagellate forms develop.

Chinese hamsters (*Cricetulus griseus*) are the most susceptible experimental animals, and succumb regularly after intraperitoneal inoculation. Monkeys, dogs, and cats are less susceptible. The pathologic changes in experimental animals are similar or identical with those in man (Meleney). One attack of kala-azar confers lasting immunity.

Transmission. Despite the most exhaustive studies, the exact mode of transmission from man to man is not known with certainty. It is highly probable that flies of the genus *Phlebotomus* transmit the parasite by their bite (Smith, Chiranji Lal, Mukerjee, and Halder). The organisms do not appear in the pharynx of the sandfly until from nine to twelve days following feeding on an infected animal. Infection from ingestion of contaminated food and from contact cannot be ruled out (Forkner and Zia). Dogs in north China and in the Mediterranean countries have a similar disease, and may represent the animal reservoir.

Incidence. Endemic foci are found in many parts of the world, notably about the Mediterranean, in India, in the Sudan, in north China, and in southern Russia. More precise pathologic studies have shown a focus in Brazil. Rural districts are more heavily infected than urban. The disease is more common in men, and in persons debilitated by other chronic infections. Infection may occur at any period of life. In the Mediterranean region and in China it is frequent in children, while in India most cases are in young adults (Scovel).

Clinicopathologic Correlation. The length of the incubation period is unknown. The mortality in untreated cases varies from 80 to 90 per cent, and the course is from a few weeks to many years. Parasitism and multiplication of monocytes lead to enlargement of the spleen, liver, and lymph nodes, readily demonstrable by clinical examination. Involvement of the bone marrow is probably responsible for the progressive anemia and leukopenia. Aside from these definite anatomic changes there are prominent signs of an acute or chronic infection—fever of an undulating type, weakness, and emaciation.

Death usually results from some secondary infection, such as noma, pneumonia, bacillary or amebic dysentery, or malaria. The reason for the increased susceptibility to bacterial infection is not known, but it is possible that the reticulo-endothelial system is so parasitized that it cannot function in the defense of the body.

Infantile Kala-Azar. It was originally thought that this disease in the Mediterranean countries was caused by a different species, designated as "*Leishmania infantum*," but this has since been disproved. Mental dullness is a conspicuous feature of the clinical course, and the enlargement of the spleen and liver is excessive.

Post-Kala-Azar Dermal Leishmaniasis. In patients receiving inadequate therapy with the salts of antimony, multiple depigmented patches and nodules may appear on the skin. In histologic sections Leishman-Donovan bodies in mononuclear cells are easily demonstrated.

African Sleeping Sickness

Two forms of sleeping sickness exist in Africa. One is East African sleeping sickness, caused by *Trypanosoma rhodesiense*, running a rapid course, ending fatally within a year, occurring in sporadic form, and found in a limited area of Rhodesia, Portuguese East Africa, Nyasaland, and the northeast part of Mozambique (Blair). The other, mid-African sleeping sickness, caused by *Trypanosoma gambiense*, runs a much longer course, ends fatally after several years, occurs in endemic and epidemic form, and is found on the west coast and central part of Africa between 15° north and 15° south latitude.

Pathologic Anatomy. The principal pathologic changes resulting from the direct action of the trypanosomes are in the lymph nodes and in the brain. During the early stages the lymph nodes are enlarged, soft, and pinkish red. There are proliferation of endothelial cells and filling of the sinusoids with monocytes. The blood vessels are hyperemic, and there is hemorrhage into the lymphoid tissue. A smear of fluid expressed from the nodes contains many trypanosomes. In the terminal stages the lymph nodes are small and firm, and microscopically show excessive proliferation of connective tissue and destruction of the architecture of the nodes.

Gross examination of the *brain* reveals an increase of slightly cloudy cerebrospinal fluid. The pia-arachnoid is slightly thickened and opaque. The convolutions are swollen and flattened, and the gyri are inconspicuous. On section the cerebral substance is soft, and throughout all parts there are petechiae, and less commonly larger hemorrhages. The meninges and the perivascular spaces of Virchow-Robin, as seen microscopically, are filled with

the same in both types of sleeping sickness, but are usually less conspicuous and less advanced in the Rhodesian than in the Gambiense form.

Lesions in the other viscera are varied, and are in large part dependent on the presence of complicating disease. There is usually slight to moderate enlargement of the liver and spleen, with focal necrosis in the liver and endothelial hyperplasia in the spleen.

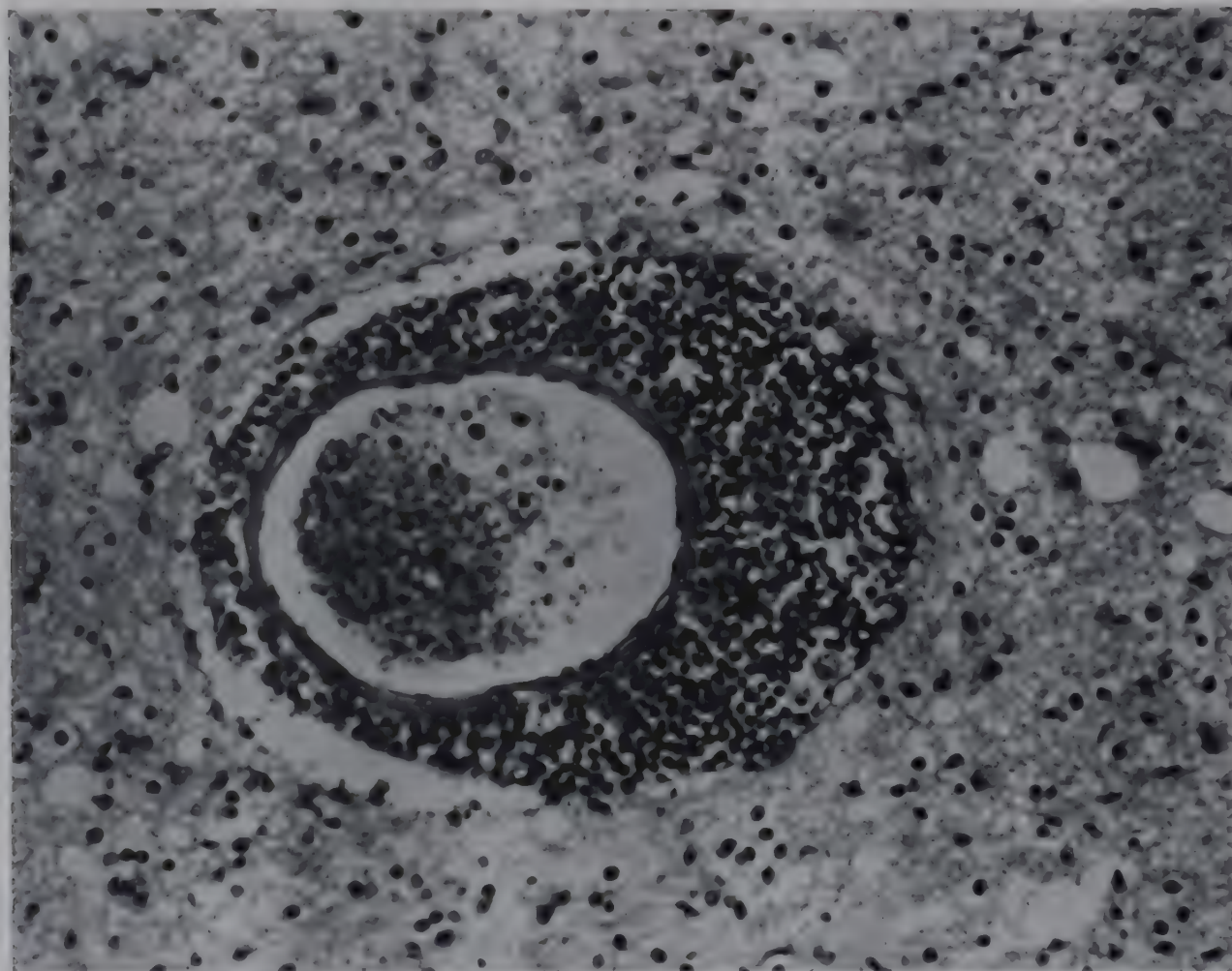


Fig. 229. Perivascular infiltration of the brain in African sleeping sickness. (Armed Forces Institute of Pathology, Neg. No. 46922.)

lymphocytes, mononuclear cells, and polymorphonuclear leukocytes. The endothelial cells of the small capillaries are enlarged and partially occlude the lumina. Within the brain, particularly about the affected blood vessels, there are accumulation of microglia and proliferation of astrocytes. Changes in the ganglion cells are minimal, and are limited to slight degeneration affecting the tigroid substance and the cytoplasm. Both in the meninges and in the brain there are highly characteristic cells, known as "morular cells." These are presumably mononuclear cells that have ingested foreign material in the form of vacuoles, each of which projects on the surface, giving the appearance of a mulberry (Bertrand, Bablet, and Sicé). These changes in the brain are

Trypanosomes are difficult to demonstrate in the tissues in the fatal cases.

Secondary Changes. In fatal sleeping sickness there are numerous complicating lesions that may obscure the typical pathologic changes. Patients are usually emaciated, and infection with worms and protozoa is common. Decubital ulcers are frequently observed, and secondary bacterial infection through these ulcers with fatal septicemia or pyemia, together with pneumonia, constitutes the terminal illness, in most patients. A major contributing factor to these secondary changes is the fact that patients are frequently abandoned by their relatives and friends to lie exposed to the elements for days or weeks before death.

Causal Agent. In man the two trypanosomes are identical in morphology. In preparations stained with Wright's stain the organisms measure 14 microns in length and 1.5 to 3.5 microns in breadth. The cytoplasm is granular

Within the host-cells the trypanosome takes on the usual leishmanial form. On inoculation into experimental animals, *Trypanosoma rhodesiense* takes on a slightly different form, with the nucleus in the posterior posi-



Fig. 230. Worldwide distribution of trypanosomiasis.

and vacuolated, and may contain volutin granules. There is a central nucleus and a posterior kinetoplast. Rising from the blepharoplast is an acidophilic flagellum which runs along the edge of the cell to form an undulating membrane.

tion, and becomes identical with *Trypanosoma brucei*. For this reason many investigators regard these two species as identical, and assume that *Trypanosoma rhodesiense* is a variety that has become adapted to man. *Trypanosoma brucei* is found in the antelope, and

causes a fatal disease of cattle known as "nagana." *Trypanosoma gambiense* and *rhodesiense* are readily grown in chick embryos and survive and multiply to a limited extent on N.N.N. media. Agglutinins and complement-binding bodies are found in the blood in variable amount. Both organisms are pathogenic for rats, mice, guinea pigs, monkeys, and dogs.

Transmission. Sleeping sickness is transmitted biologically from man to man by tsetse flies belonging to the genus *Glossina*. Rarely the transmission is mechanical, on the soiled proboscis. It is possible that other insects, such as mosquitoes, ticks, bedbugs, and lice, may mechanically transmit the trypanosomes. Blood containing trypanosomes is sucked into the gastro-intestinal tract of *Glossina*. After ten to fifteen days the organisms reach the salivary glands. Gambian sleeping sickness is usually transmitted by *Glossina palpalis*, and Rhodesian by *Glossina morsitans*. Rare methods of transmission of the Gambian type are by coitus, congenitally through the placenta, and by ingestion of milk from an infected mother.

Sex, age, race, and social status apparently have no influence on the incidence of the disease. A definite animal reservoir for *Trypanosoma gambiense* has not been identified, but domestic animals, such as goats, cows, and sheep, may carry the organisms for long periods, and must be recognized as potential reservoirs. The reservoir of *Trypanosoma rhodesiense* is the antelope, in which animal no disease is produced.

Clinicopathologic Correlation. The incubation period varies from seven to twenty-one days, and there follows a period of weeks or months in which there are many parasites in the blood, and gradual enlargement of the lymph nodes, particularly those in the neck. After some months invasion of the nervous system gives rise to changes typical of sleeping sickness. At first these are consistent with a mild inflammation—headache, fever, and drowsiness. Later there are the symptoms of profound involvement of the brain, without localization. A few persons recover during the early stages, and carriers exist. The mortality before the introduction of modern drugs for therapy was 100 per cent, after invasion of the central nervous system. With trypanamide the mortality, even if the treatment is begun late, should not exceed 25 per cent.

From 9 to 25 per cent of the population of some districts of Africa suffer from the condition, and 20 to 30 per cent of all deaths in central Africa are from sleeping sickness (Kellersberger).

Trypanosomiasis in Animals. In addition to *Trypanosoma brucei*, the cause of nagana, there are *Trypanosoma evansi*, causing surra in horses; *Trypanosoma equiperdum*, responsible for a venereal disease in horses; and *Trypanosoma lewisi*, found in the blood of wild rats throughout many parts of the world. The latter species has been extensively used in experimental work on trypanosomiasis. There is a single, apparently acceptable, report of an infection of man with *Trypanosoma lewisi* (Johnson).

Chagas' Disease

Pathologic Anatomy. The principal pathologic changes in Chagas' disease, caused by *Trypanosoma cruzi*, are in the heart. It is dilated and flabby, and the muscle is pale and soft. Microscopically, the individual muscle fibers are seen to be greatly enlarged and heavily parasitized with leishmanial forms of the trypanosome. Until rupture of the encysted organism the muscle fiber is not greatly altered (Kean). There is an intense infiltration with lymphocytes, plasma cells, mononuclear cells, and an occasional eosinophil. In all of the serous cavities there is an accumulation of a transudate, and there is edema of the subcutaneous tissues. In the viscera, notably the liver, spleen, and kidneys, there is moderate to advanced chronic passive hyperemia, with degenerative changes in the cells or fibers dependent on the duration of the failure (Fig. 231). A unilateral, purulent type of conjunctivitis is a frequent finding. The brain grossly shows no change, but microscopically small foci of glial proliferation, with parasitism by leishmanial forms, may be seen (Lundeberg).

Causal Agent. *Trypanosoma cruzi* is a pleomorphic trypanosome, and may occur in either motile or leishmanial forms. In the blood of man it is a spindle-shaped trypanosome measuring 25 microns in length. In the myocardium and in other tissue cells the leishmanial forms are round or oval, and measure from 1.5 to 4 microns in diameter. In the transmitting insects the organism has the usual morphology

of leptomonas, crithidial, metacyclic trypanosomes. It has been cultured on N.N.N. media. The diagnosis is based on the identification of the trypanosome in the blood during the acute stage of the disease. Agglutinins and complement-binding bodies are present. An immunity transmitted from mother to offspring can be demonstrated in experimental animals (Kolodny).

Transmission. The infection in man is spread by rubbing the feces of the transmitting insect into an abrasion or bite on the

and destruction of the heart, with consequent cardiac failure. In children the disease is usually acute and runs a course of two to four weeks, while in adults it is more chronic. The mortality is high after the development of clinical signs, and there is no satisfactory treatment (Moseley and Miller).

Trichomonadal Vaginitis

Within the vagina in trichomonadal vaginitis there is a frothy mucopurulent dis-



Fig. 231. Heart in Chagas' disease. (Armed Forces Institute of Pathology, Neg. No. 60817.)

skin. In Brazil the insect vector is the reduviid bug, *Panstrongylus megistus*. Other similar insects serve as the vectors in Guatemala and Panama. The animal reservoirs include the South American armadillo, Panamanian bat, opossum, wood rat, and certain species of monkeys (Wood and Wood). Dogs, cats, rats, mice, and guinea pigs are susceptible to experimental inoculation (Clark and Dunn). Chagas' disease is endemic in northern South America, Panama, and Guatemala, and may exist in the southern United States (Wood).

Clinicopathologic Correlation. The incubation period varies from seven to fourteen days. Human carriers probably exist, since trypanosomes have been found in the blood of persons free of symptoms. The clinical manifestations in large part depend on the invasion

charge. The mucous membrane is swollen and red. In some patients there are similar changes on the vulva and in the bladder. Microscopically, ulceration of the epithelial surface and dense infiltration of the underlying tissue with lymphocytes and polymorphonuclear leukocytes are seen (Adair and Hesselstine). *Trichomonas* has been cultured free of bacteria, and on experimental inoculation into the vagina of women has produced the complete clinical and pathological picture (Trussell and Plass). It is an organism of low virulence with no invasive power and has no influence on puerperal mortality.

Giardiasis

In the United States about 5 per cent of adults and 20 per cent of children are infected

with *Giardia lamblia*. Whether or not disease is produced by the presence of the parasite is controversial, but many of the infected persons complain of diarrhea, abdominal distress, nervousness, fever, and vomiting. Autopsy observations are so few that it is not possible to describe any typical pathologic change (Nutter, Rodaniche, and Palmer).

Malaria

The name "malaria" is derived from the colloquial Latin *mala* (bad) and *aria* (air),

tree" (an early author misspelled the Countess' name); discovery of the parasite in the blood of patients on November 6, 1880, by Laveran; and the postulation by Manson in 1894 of the transmission of the disease by mosquitoes and experimental proof of this postulation by Ross in 1897.

Pathologic Anatomy. The pathologic changes in malaria are concerned with four basic processes: hypertrophy and hyperplasia of the reticuloendothelial cells of the body, the elaboration of a characteristic pigment by the malarial parasites, the blockage of capil-

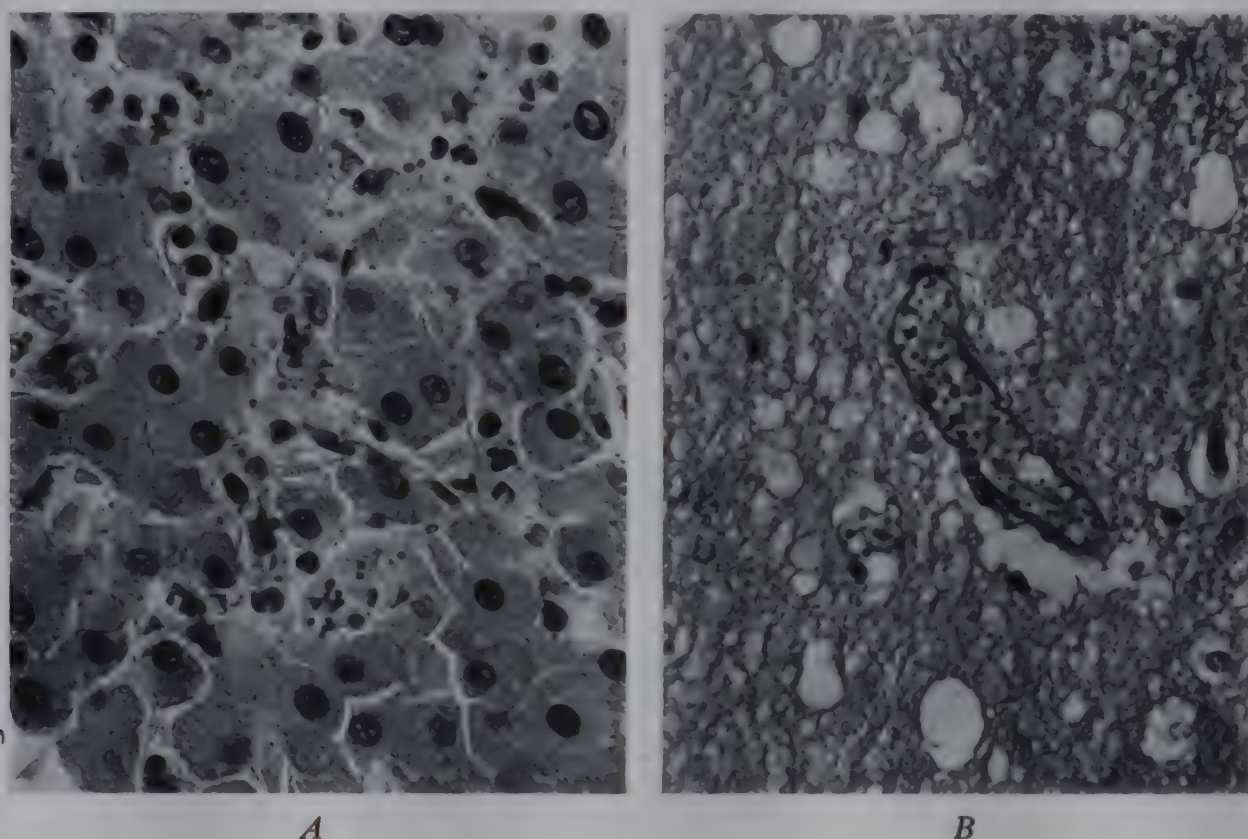


Fig. 232. *A*, Pigment in Kupffer cells of liver in malaria. *B*, Heavily parasitized blood in cerebral capillary in malaria.

and symbolizes the older idea of the nature and cause of the disease. It is today the most important and most common infectious disease, and probably the most important of all diseases in the world. In 1932 the League of Nations stated that 17,750,760 cases of malaria had been treated in 65 countries during the preceding year. It is estimated that there are 100,000,000 persons with malaria in India, out of a population of 353,000,000. It has been directly responsible for the depopulation of large areas of the earth, and is hindering the development of others.

Outstanding events in the history of our present knowledge of malaria are: the supposed treatment in 1636 of the Countess of Chinchon, wife of the viceroy of Peru, for a periodic fever, with an extract of the bark of a tree, subsequently named the "cinchona

laries by parasitized red blood cells, and secondary effects of the destruction of red cells. The pathologic appearance of the organs is slightly different in acute and chronic varieties, and they will be described separately.

Acute Malaria. The spleen is moderately enlarged and soft to diffuent in consistency. The capsule is not thickened, and there is no increase in fibrous tissue throughout the pulp. The malpighian bodies may or may not be discernible as elevated gray, slightly firmer nodules. The color in general is dark red, with a gray or brown element. Microscopically, the sinusoids are seen to be distended with red blood cells and large mononuclear cells. The red cells contain numerous parasites, and the phagocytic cells are filled with fine granules of brown or black pigment. The liver is usually enlarged and grayish brown. Microscopically,

hyperplasia of the Kupffer cells and distention of their cytoplasm with pigment are observed (Fig. 232, *A*). Many of the sinusoids are completely blocked.

In the brain the cortex is frequently a peculiar slate-gray color and throughout both the cortex and the white matter there are numerous petechiae. As seen microscopically the capillaries are distended, and many are completely occluded by agglutinated parasitized red cells. Within the endothelial cells of the capillaries there are numerous granules of pigment (Fig. 232, *B*). About the occluded capillaries the perivascular space is filled with red cells (Rigdon). The bone marrow, especially that of the trunk, is red and fleshy, and microscopically shows a normoblastic type of hyperplasia. The endothelial cells of the sinusoids are prominent and are filled with pigment.

Changes in the other viscera are variable. Small foci of necrosis incident to occlusion of the capillaries have been observed in the adrenals and in the intestinal mucosa. Occasionally the heart is the seat of a profound fatty degeneration and interstitial myocarditis similar to that seen in diphtheria. Pigmentation of the mucosa of the small intestine occurs (Helpern).

Chronic Malaria. The outstanding pathologic change in chronic malaria is the enlargement of the spleen, the "ague cake" of colloquial medical terminology. The spleen weighs from 500 to 2000 gm. The capsule is thickened, gray, and opaque, and the organ cuts with increased consistency. Microscopic inspection reveals proliferation of fibrous tissue in the pulp cords, and large numbers of mononuclear cells infiltrated into the fibrous tissue and the pulp cords. The malpighian bodies are inconspicuous and small. Within and about them are extensive deposits of the malarial pigment. The liver is moderately enlarged and weighs about 2000 gm. Microscopically, hyperplasia of the Kupffer cells and deposit of the same pigment within them are seen.

In the bone marrow there are prominent hyperplasia of the reticuloendothelial cells and normoblastic hyperplasia of the erythropoietic tissue in direct proportion to the degree of the anemia. In the heart there is fatty degeneration, especially marked in the left ventricle, incident to the anemia. Similar degenerative changes may be found in the

hepatic cells and in the renal epithelium. The brain shows atrophy and a slate-gray pigmentation of the cortex. Microscopic study shows atrophy of ganglion cells and abundant pigment granules in the endothelial cells. General inspection in chronic malaria reveals an emaciated person, with depletion of the subcutaneous fat and atrophy of the muscles, which are pale and flabby.

Physiologic and Chemical Aspects. In both acute and chronic malaria there is a decrease in the total plasma protein, more evident in the albumin, and often accompanied by actual increase of globulin. The melanoflocculation test for the diagnosis of malaria utilizes the latter change. The pathologic changes in the liver bring about some disturbance of hepatic function, as tested with galactose or other substances. Immediately following rupture of many red blood cells, excessive amounts of potassium are released, and the value for serum potassium may be increased as much as 50 per cent for a period of several hours.

The Malarial Pigment. Most studies show that there are two pigments in the tissues in malaria; one contains stainable iron and the other does not. There is some evidence that the latter is the pigment derived from hemoglobin by the parasite, and that after phagocytosis by mononuclear cells it is oxidized to the former (Rigdon).

Causal Agent. There are three important and two relatively unimportant plasmodia that produce malaria in man. The three are *Plasmodium vivax*, producing tertian malaria; *Plasmodium malariae* of quartan malaria; and *Plasmodium falciparum* of malignant or estivo-autumnal malaria. *Plasmodium ovale* is responsible for a disease resembling tertian malaria, and *Plasmodium knowlesi*, a normal pathogen of the monkey, has been used in the treatment of paresis.

All plasmodia pass through an asexual cycle in the intermediate host, man, and a sexual cycle in the definitive host, the mosquito. In man the parasite goes through several stages, known chronologically as the "trophozoite," the "schizont," the "merozoite," and the "gametocyte." This development is known as "schizogony." With Wright's stain the trophozoite appears as a small, blue-stained ring of cytoplasm with a red dot of chromatin. As the plasmodium enlarges, the ring structure is lost, and it appears as a blue-

stained body of irregular contour, containing dots or threads of red-stained chromatin and granules of pigment. Gradually the parasite becomes definitely oval or round, with large granules of chromatin and abundant pigment—the schizont. Eventually the parasite fills the greater part of the cell and divides into numerous small oval or round blue bodies, each having a bright red chromatin dot—the merozoite. At this point the red blood cell ruptures, and the merozoites are liberated into the circulating blood. Some of them invade other red blood cells and repeat the cycle. Others are phagocytized and destroyed by the reticuloendothelial cells.

The differentiation of the three important species is based upon a number of characteristics, summarized in Table 25. Texts of parasitology should be consulted for minute descriptions and for differentiation of trophozoites, schizonts, merozoites, and gametocytes of the three species.

Immunity. There is certainly an acquired immunity in malaria, and probably also some natural immunity. This immunity is based on both humoral and cellular factors. It develops slowly, and only after several relapses and remissions. Thus, in one series studied, 34 per cent became immune after the first infection. 72 per cent after the second, 87 per cent after

TABLE 25. DIFFERENTIATION OF TYPES OF MALARIA

	Plasmodium vivax	Plasmodium malariae	Plasmodium falciparum
Duration of schizogony	48 hours	72 hours	26 to 48 hours
Invasion of red blood cells . .	Parasite occupies the entire enlarged cell	Parasite occupies almost the entire not enlarged cell	Parasite occupies $\frac{2}{3}$ to $\frac{3}{4}$ of the not enlarged cell
Onset of fever	Usually sudden	Usually sudden	Insidious or sudden. Chills may be absent
Duration of paroxysm	6 to 8 hours	4 to 6 hours	12 to 26 hours
Duration of fever in an untreated attack	2 to 4 weeks	4 to 8 weeks	10 days to 12 weeks

After three to four asexual cycles of this type some trophozoites develop into macrogametocytes and microgametocytes, the female and male sexual forms respectively. Gametocytes are round or oval masses of basophilic cytoplasm, with a central spherical mass of deep red chromatin. The gametocytes are sucked up by a biting mosquito, and the cycle to be described in a later paragraph takes place within the tissues of the definitive insect host. Plasmodia have been cultivated on artificial media, but die out after a few generations. It is probable that none of the species infective for animals and birds, with rare exceptions, are pathogenic for man. This means that there is no animal reservoir, and that malaria continues as an endemic disease because of latent cases in man. It is possible that the chronicity of the disease is the result of an as yet unproved exo-erythrocytic stage of the disease (Shortt and Garnham).

the third, and 100 per cent after the fourth. If the disease is terminated by treatment with drugs early in the first attack, there is little demonstrable resistance to a second infection. By different techniques, protective antibodies, agglutinins, and complement-binding bodies can be demonstrated in the serum. Cellular resistance is largely dependent on the more rapid mobilization of larger numbers of phagocytic cells in the immune animal (Taliaferro). Of considerable interest is the observation that most patients with malaria during the acute stage have positive Wassermann and Kahn reactions. The reason for this is not clear.

Transmission. Malaria is transmitted from man to man by the bite of the female anopheline mosquito. In North America the principal transmitters are *Anopheles quadrimaculatus*, *Anopheles accidentalis*, and *Anopheles freeborni*. In the Caribbean area the most

important vector is *Anopheles albimanus*. With the advent of the airplane, *Anopheles gambiae* was brought from Africa to the bulge of Brazil, and was responsible for an especially virulent type of malaria in that region during the 1930's. The *Anopheles* mosquitoes are rarely found at a distance greater than one mile from their breeding grounds, and are most numerous on the fringes of human habitation; that is, in the suburbs of larger cities. After ingesting infected blood a mosquito may remain infective for periods up to about ninety days. Parasites are not transmitted in the mosquito from one generation to another.

The mosquito takes up the male and female gametocytes from the blood of man, and their development in the mosquito is known as "sporogony." In the stomach of the insect the microgametocytes throw out motile, threadlike filaments, four to six in number. The macrogametocytes extrude a certain amount of chromatin, and are then ready for fertilization. The mature gametes fuse, and the resulting structure is known as a "zygote." The zygotes elongate, become motile, and are designated as "ookinetes." The parasite at this stage penetrates the epithelial lining of the stomach, becomes spherical in shape, forms a cyst between the epithelium and the elastic membrane, and is called an "oocyst." Numerous small, slender, spindle-shaped bodies, sporozoites, form within the oocyst. Sporozoites are liberated into the body cavity by rupture of oocyst, and invade all of the tissues of the mosquito, especially the cells of the salivary glands and the salivary ducts. When an infected mosquito bites a man, the sporozoites are injected into the wound and the cycle is complete.

In addition to the usual biological transmission, malaria has been transmitted from man to man by direct inoculation of blood, either deliberately in the treatment of paresis, or accidentally in "main-line" drug addicts. Congenital transmission of the disease from mother to fetus has been observed.

Incidence. Geographical Distribution. Malaria is worldwide in distribution, in general in a belt from 45° north to 40° south latitude. *Plasmodium vivax* is most widely distributed, occurring as far north as 60° and as far south as 20°. It is the prevailing species in the Temperate Zone. *Plasmodium malariae*, a comparatively uncommon species, is found in cen-

tral Europe, about the Mediterranean, in the Near East, in the Orient, and in tropical regions in Africa and Central America. *Plasmodium falciparum* is the prevailing species in most tropical countries of both the Eastern and Western Hemispheres and in central Europe. *Plasmodium ovalis* is found only in the Philippines and in Africa. The incidence of malaria differs with race, age, sex, occupation, locality, climate, nature of the soil, moisture, and altitude, so far as these factors bear upon conditions favorable for the breeding of the anopheline mosquitoes and the opportunity of the mosquitoes to bite man. This is well illustrated by the greater incidence in men than in women, purely because of greater exposure.

The importance of malaria in military campaigns is well illustrated in the Allied occupation of Salonica in 1916. The Allies landed 115,000 troops, and within a year 60,000 of them had acquired malaria, and at any one time not over 20,000 effectives were available to man the trenches. Systematic prophylaxis with quinine was initiated in 1917, and vigorously pushed in 1918. The morbidity and mortality of malaria fell precipitously. A point frequently overlooked by engineers is the development of breeding grounds for mosquitoes in the construction of hydroelectric plants. Fortunately the Tennessee Valley Authority of the United States Government is well aware of this danger, and a systematic campaign has been undertaken to eradicate the created breeding grounds.

Clinicopathologic Correlation. The incubation period varies from ten to seventeen days. Tertian malaria in general is a mild disease, while estivo-autumnal malaria is severe. At the time of the rupture of the red blood cell and liberation of merozoites the patient experiences a chill followed by fever. It is estimated that this chill will result from the parasitism of one out of every hundred thousand red blood cells, representing a total of 150,000,000 parasites in a man of average size. The usual degree of parasitism varies from 20,000 to 500,000 infected red cells per cubic millimeter of blood. The higher degrees of parasitism carry with them a greater mortality.

The destruction of the red blood cells leads to a normocytic or microcytic anemia, which in turn is probably responsible for the weakness, fatigability, and emaciation of the per-

son with chronic malaria. The hyperplasia of the mononuclear cells in the viscera is reflected in an increase of monocytes in the peripheral blood, reaching values as high as 25 per cent of all the white cells. The progressive occlusion of small capillaries by agglutinated cells

cretion of large amounts of albumin, retention of water, and edema, but without retention of the nitrogenous metabolites. It usually clears up on antimalarial treatment.

The relation of malaria to the occasional sequela, chronic glomerulonephritis, is not



Fig. 233. Worldwide distribution of malaria.

brings about impairment of function of many organs, and mental deterioration. Lesions of the kidneys, except in blackwater fever, are usually transient, and the result is only a slight albuminuria. Rarely in acute malaria there is a peculiar type of nephrosis with ex-

clear. The liberation of large amounts of potassium from the red cells may be responsible for the occasional symptoms of adrenal insufficiency. The occlusion of the capillaries of the adrenal and toxic necrosis of the cortical cells is probably also a contributing factor. En-

largement of the spleen and liver brings about conspicuousness of the abdomen and a sense of fullness.

The characteristic features of untreated malaria are latency and relapses. In a person with latent malaria the injection of a vasoconstrictor substance such as epinephrine leads to contraction of the spleen and the ejection of parasites into the blood. The mortality rate in untreated malaria varies from 1 to 4 per cent; in the cerebral types the mortality may reach 50 per cent; and in the malignant varie-

excreted in the bile. A peculiar combination of hematin and albumin, known as "methemalbumin," is present in large amounts in the serum of patients with blackwater fever, and in small amounts in the serum of most persons with malaria.

The pathologic changes are essentially those of severe active malaria plus the lesions of extensive intravascular hemolysis—cloudy swelling and necrosis of the renal epithelium, hemoglobin casts in the renal tubules, active erythrophagocytosis in the reticulo-endothelial



Fig. 234. Balantidial dysentery. Note organisms in submucosa. (Armed Forces Institute of Pathology, Neg. No. 38159.)

ties of estivo-autumnal malaria the mortality averages 25 per cent. Both the morbidity and the mortality of the disease have been greatly reduced by prophylaxis and treatment with antimalarial drugs. In the United States Army the morbidity from malaria fell from over 200 per thousand troops in the middle of the nineteenth century to less than 2 per thousand in the 1930's (Simmons).

Blackwater Fever. In some patients with malaria, usually falciparal, there is massive intravascular hemolysis and the liberation of large amounts of hemoglobin in a period of a few hours. Part of the hemoglobin is excreted by the kidneys in the form of a red or black urine—hence the name "blackwater fever." The remainder is converted into bilirubin and

cells, and distention of the bile canaliculi of the liver.

Many varieties of mammals and birds and even a few reptiles suffer from a natural disease similar or identical to malaria in man.

Balantidiasis

The protozoon, *Balantidium coli*, may be found in the stools of apparently healthy persons, but it may cause clinical symptoms and even death. There is a catarrhal, ulcerative colitis. Further invasion of the body apparently does not occur. In most instances of dysentery associated with *Balantidium coli* there is secondary infection, and it is not possible to determine how much of the change

is caused by the bacterium (Walker). Man is infected by swallowing the cysts in contaminated food. The use of the excrement of swine as fertilizer may be the source of the contamination.

Toxoplasmosis

Pathologic Anatomy. The anatomic changes of toxoplasmosis are somewhat different in infants and adults (Callahan, Russell, and Smith).

filtration—and maximal changes in other tissues. In addition to the granulomatous lesions described in infants there is a distinctive pneumonia. The alveoli are lined with parasitized cuboidal cells and the alveolar spaces are filled with fluid and mononuclear cells. The alveolar walls are edematous (Pinkerton and Henderson).

Causal Agent. *Toxoplasma* is a protozoan, but its exact classification is not yet determined. It is crescentic in shape and 4 to 7 microns in length and 2 to 4 microns in width.

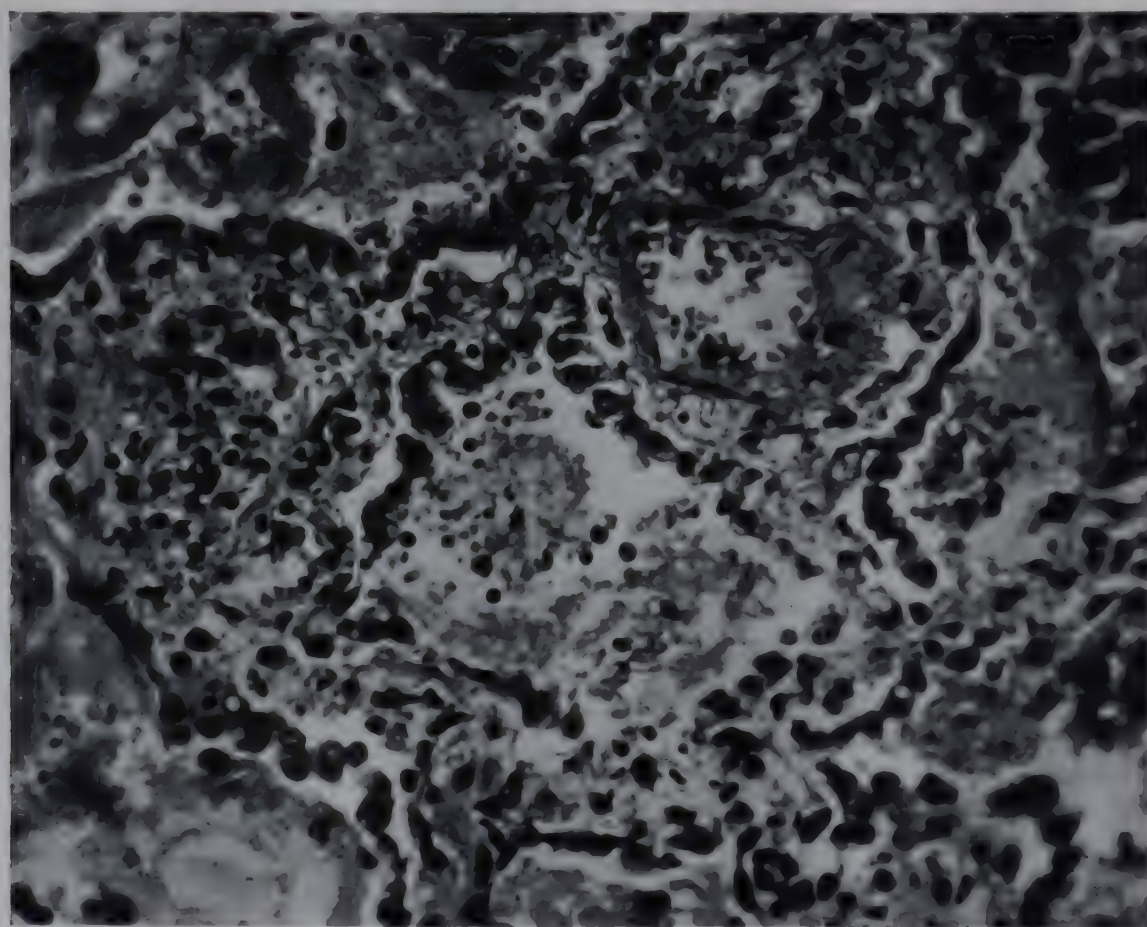


Fig. 235. Pneumonia in toxoplasmosis. (Slide by courtesy of Dr. Henry Pinkerton.)

Infantile Type. The outstanding lesions are in the brain but changes are observed in many other organs. In the gray matter of all parts of the brain and spinal cord there are focal lesions varying from infiltration with leukocytes, lymphocytes, and plasma cells to necrosis and cyst formation. In many foci of necrosis there is calcification. In other organs, notably the heart, lungs, adrenals, liver, and spleen, there are small granulomatous lesions with or without central necrosis. Pulmonary changes may be those of an interstitial pneumonitis. The retina and choroid of the eye show degenerative and inflammatory changes. Organisms are present in all lesions.

Adult Type. In contrast with the infantile type, toxoplasmosis in adults exhibits minimal changes in the brain—slight perivascular in-

There is a distinct nucleus. Neutralizing antibodies are present in the serum during active disease and after recovery (Callahan).

Transmission. There are apparently two types of toxoplasmosis—congenital and acquired. In the congenital type infection occurs in utero. This may lead to fatal disease in infancy or latent disease which in a woman is passed on to her children. Where the organisms are carried is unknown, but possible toxoplasma in myocardial fibers have been described as incidental autopsy findings (Plaut).

Clinicopathologic Correlation. The manifestations of the changes in the nervous system include hydrocephalus and convulsions. The calcification may be seen on radiographs. The chorioretinitis is readily observed with an ophthalmoscope (Wagener). Other signs

and symptoms vary with the organ involved. Callahan found neutralizing bodies in the serum of 2.7 per cent of individuals in the St. Louis area.

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Diseases Caused by Helminths

The word helminth is derived from the Greek, meaning worm, and refers to worms of all varieties included in two phyla: Nemathelminthes, or roundworms, and Platyhelminthes, or flat worms.

The true roundworms of the class Nematoda are the only species of the phylum Nemathelminthes of interest to the human pathologist. The important genera are: Trichinella, Trichocephalus, Strongyloides, Ancylostoma, Necator, Enterobius, Ascaris, Wuchereria, Onchocerca, and Dracunculus. Two classes of the phylum Platyhelminthes, Trematoda and Cestoda, are of interest in medicine. The important genera of Trematoda are: Schistosoma and the various species of flukes. Important genera of Cestoda are: Diphylobothrium, Hymenolepis, Taenia, and Echinococcus.

General Incidence of Intestinal Helminths. The incidence varies in different parts of the world, and depends on climatic and sanitary conditions. The important climatic factors are rainfall (Spindler), type of soil (Augustine and Smillie), and temperature. Notable sanitary factors are the use of human excreta for fertilizer (for example, in China), and the careless disposal of human excreta in latrines and outhouses.

Effect of Age, Sex, and Race on Incidence of Infestation. In general, infestation with worms is well established by the age of three to six years, and remains about constant until the age of forty, when it decreases in incidence (Faust and Headlee). There are no significant differences in the general incidence of infestation between the sexes, but some specific worms, such as hookworm, show a higher incidence in boys than in girls. In the case of hookworm Smillie and Augustine have demonstrated a much higher incidence of infestation in whites than in Negroes.

Parasitism versus Pathogenism. It is evident from the figures on the incidence of infestation with helminths that many persons carry these worms in their gastro-intestinal tracts and suffer no ill effects. If there are only a few worms there are frequently no signs or symptoms. Thus one must distinguish between infestation with a worm and disease caused by a worm.

General Pathologic Changes. All worms, including those confined to the gastro-intestinal tract and those which invade the tissues of the body, produce their effects in three general ways: through mechanical irritation, through loss of blood or lymph, and through the action of toxic substances. Within the gastro-intestinal tract they may produce partial or complete obstruction, or their mere presence may irritate the musculature so that diarrhea or cramps are produced. In the tissues there is proliferation of fibrous tissue about the worms. The loss of blood and lymph occurs largely with the intestinal worms. They become attached to the wall, open blood vessels, and lymphatic vessels, and ingest the blood. The toxic factor is extremely difficult to prove. With the broad tapeworm there is considerable evidence that a toxic substance is responsible for the macrocytic anemia. In dracunculosis there is a severe systemic reaction at the onset of the disease, similar to that produced by histamine.

Life Cycles. Control. Auto-infection. Life cycles of the helminths are simple or complex. In the simple type, typified by Enterobius vermicularis, the eggs passed in the stool are ingested by the same or another human being, and infection is thereby carried on from man to man. In the complex type, typified by Diphylobothrium latum, there are two intermediate hosts which are necessary for the completion of the cycle, and contagion from man

to man is unusual. From the standpoint of pathogenesis there are two methods of invasion of the gastro-intestinal tract, a simple and a complex. In the simple, as with *Trichocephalus trichiuris*, the eggs ingested with the food develop directly into adult worms within the gastro-intestinal tract. In the complex type, as with *Ascaris* and *Necator*, the larvae are found in the soil. They invade the skin of the foot or other exposed part, are carried to the lung, and wander into the bronchi and trachea, and thence into the esophagus and intestine. The resistance of the human body to most intestinal helminths is high, and withdrawal of the con-

worms, each surrounded by a focus of fibrosis and slight infiltration with lymphocytes and eosinophils, are observed. It must be assumed that these represent a subclinical infection. Recently surveys in various parts of the United States have shown that *Trichinella* is present in the muscles of about 16.1 per cent of all adults (Wright and Walton).

Clinical Trichinelliasis. In active trichinelliasis female worms are present within the crypts of the duodenum, or have invaded the wall down to the muscularis. The skeletal muscles are pale and swollen, and throughout them small white or red foci may be seen

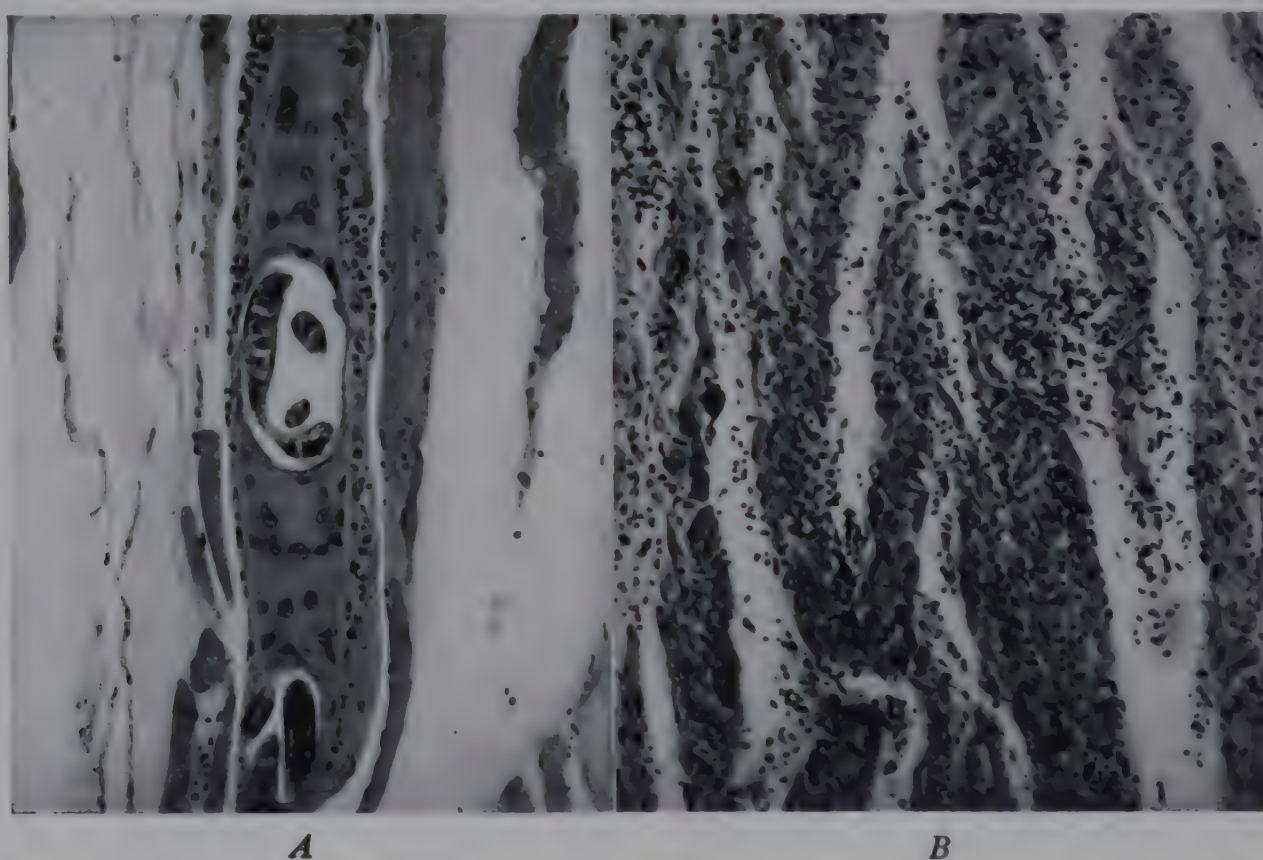


Fig. 236. Trichinelliasis. *A*, Parasite in a skeletal muscle fiber with multiplication of nuclei. *B*, Myocarditis. (Tissue by courtesy of Dr. Donald Parker.)

stant infection will result in a cure. If a child with round worms is removed to a sanitary environment the worms disappear from the intestine within a few months.

Trichinelliasis

Trichinelliasis or trichinosis is a condition caused by invasion of the tissues with a nematode, *Trichinella spiralis* (Gould).

Subclinical Trichinelliasis. Trichinelliasis was first observed in the dissecting room, where anatomists noticed white calcified nodules, 1 to 1.5 mm. in diameter throughout the skeletal muscle (Blumer). In addition to the calcified nodules, partly or fully preserved

grossly. The typical coiled worms may be seen microscopically in the fibers. The immediately surrounding connective tissue is edematous and infiltrated with lymphocytes and eosinophils. In severe infections any organ or tissue may be affected, but the heart and the brain are the most important. The heart is pale, flabby, and dilated. There may be petechiae or ecchymoses in the pericardium, endocardium, and myocardium (Terry and Work). The microscopic picture is similar to that of the skeletal muscle, except that the worms do not encyst, and most larvae are necrotic and cannot be identified with certainty (Dunlap and Weller). Throughout the interstitial tissue of the myocardium there is

a heavy infiltration with lymphocytes and an occasional eosinophil. The brain shows little gross change except hyperemia. Microscopically a diffuse infiltration with lymphocytes in the leptomeninges and in the spaces of Virchow-Robin is seen. In nodules of lymphocytes and glial cells within the brain necrotic and living larvae may be identified. The other viscera may show cloudy swelling and fatty degeneration.

Transmission. Man contracts trichinelliasis by the eating of pork and pork products containing larvae. The cyst is digested in the stomach, and the liberated larvae develop into adult worms in the duodenum, where after copulation the female worm burrows into the wall and deposits eggs. Some larvae pass out into the lumen of the gastro-intestinal tract, but most invade the blood or lymph and are carried through the lungs into the systemic circulation. Muscles poor in glycogen are more readily invaded. Calcification occurs in about six months, and may be accelerated by the administration of vitamin D and calcium. Wild rats are the animal reservoir, but a satisfactory explanation has not yet been offered for the propagation of trichinelliasis in hogs and man. It is possible that the consumption of human uncooked garbage by hogs is responsible for some of the disease in these animals (McNaught and Zapata). Trichinelliasis is an endemic and epidemic disease of the United States and Europe. Rare cases are observed in northern Africa and in South America.

Clinicopathologic Correlation. During the first stage of the disease, lasting from one to two days, the worms develop in the intestine, causing the usual signs and symptoms of intestinal helminthism: anorexia, vomiting, diarrhea. The second stage, invasion of the blood and dissemination, gives rise to fever, and the inflammation in the muscle produces pain and tenderness. The inflammation of the heart leads to hypotension and cardiac failure (Polley and Murphy). From invasion of the tissues about the eye and face there is edema. Larvae may be found in the blood (Dammin) or in the spinal fluid (Evers; Hassin and Diamond). The most satisfactory diagnostic sign at this time is the finding of larvae in a biopsy of the deltoid muscle. The degree of eosinophilia is variable. The third stage corresponds with the encystment of the para-

site and gradual subsidence of the evidences of inflammation in the muscles, lasting about six weeks. With recovery, there are no residual signs or symptoms (Bercovitz).

Trichuriasis

Pathologic Anatomy. In minimal infections with *Trichuris trichiura* there are few, if any, changes in the intestine. In severe infections the outstanding pathologic changes are those of a severe anemia. Within the cecum there are many worms. The mucous membrane is pale or hyperemic and swollen. Microscopically minute ulcerations and infiltration with lymphocytes and eosinophils are seen. The viscera are pale, and there is fatty degeneration of the heart, liver, and kidneys (Musgrave and Clegg).

Transmission. The life cycle of the whipworm is of the simple type. Distribution is worldwide, but the whipworm is more common in moist, warm climates.

Clinicopathologic Correlation. Slight infections give no signs or symptoms. In severe infections there is diarrhea, presumably caused by the presence of the parasites in the cecum. The cause of the anemia and the nervous symptoms is not clear. The degree of eosinophilia is variable (Getz).

Strongyloidiasis

Pathologic Anatomy. In mild infections with *Strongyloides stercoralis* the mucosa of the duodenum, jejunum, and ileum is swollen, red, and soft. In more severe infections there is focal or confluent ulceration. The mucosa of the pancreatic and the common bile ducts may show similar change. Other organs and tissues rarely show pathologic change except during the period of primary invasion. Microscopically in the intestine during the early stages edema of the mucosa can be seen. In the crypts of Lieberkühn and extending into the stroma of the villi are the characteristic female worms and oviposited eggs. There is little or no inflammatory reaction except in severe infections, when there is infiltration with lymphocytes, polymorphonuclear leukocytes, and eosinophils. If there is ulceration there is usually an infiltration of leukocytes, probably in response to secondary bacterial invasion. After a lapse of some weeks or months each worm in the tissues is surrounded

by a sheath of fibroblasts two to three cells thick. There are a few mononuclear cells, occasional epithelioid cells and a rare giant cell in the surrounding tissue. Invasion below the muscularis mucosa has not been observed. In severe cases similar pathologic changes are found in the ileum and colon (Faust; Hartz).

Transmission. Filariform larvae of *Strongyloides* first penetrate into the epidermis and dermis along the hair shafts or through the crevices in the epidermis, and the tissue about each larvae is edematous and hyperemic. Small hemorrhages in the tissue are the rule.

migrate to the lumen of the intestine and are carried downward with the fecal stream (Faust). Completion of the cycle proceeds by indirect development, direct development, or hyperinfection. Indirect development occurs in warm, moist climates, and may go on for several generations outside the body of the host. In direct development the larvae in the stool transform directly into filariform larvae and are immediately infective. In hyperinfection the rhabditiform larvae metamorphose into dwarf filariform larvae, invade the mucosa of the rectum or skin about the anus, and start a new cycle. The worm is cosmopoli-



Fig. 237. *Strongyloides* in the intestine. (Armed Forces Institute of Pathology, Neg. No. 74222.)

Many larvae remain in the skin with resulting proliferation of fibrous tissue, but others migrate to the blood vessels and are carried to the lung. As they migrate out of the capillaries into the alveolar spaces there is hemorrhage into a small group of alveoli, and lymphocytes, monocytes, and leukocytes are attracted to the focus. The epithelial cells of the alveoli are desquamated. Some of the larvae invade the mucosa of the bronchi and trachea and establish a parasitic existence in these tissues. As a consequence ova are occasionally found in the sputum. Other larvae are carried to the upper intestine, where the female worms invade the mucosa and bring about the pathologic changes which have been described.

The eggs laid in the tissue of the mucosa

tan in distribution, but is not common in tropical countries.

Clinicopathologic Correlation. In most patients with a slight infection there are few clinical changes. The invasion of the colon and the onset of hyperinfection give rise to the signs and symptoms of a severe inflammation of the lower intestinal tract: diarrhea, blood in the stool, dehydration, and loss of weight. In most infections there are a leukocytosis up to 25,000 and a conspicuous eosinophilia, as high as 40 per cent.

Ancylostomiasis

Pathologic Anatomy. Typically the first 50 cm. of the jejunum is involved. The wall is thickened by edema of the submucosa and

cellular infiltration. The mucosa shows lesions varying from petechiae through ulceration to gangrene and is infiltrated with leukocytes and eosinophils. There is a lymphangitis in the submucosa and the mesenteric nodes are enlarged. Pieces of mucosa are clamped in the mouth of the worms (Fig. 238). The heart is dilated and sometimes hypertrophic, and the myocardium usually shows advanced fatty degeneration. In the liver and kidneys there is slight to moderate fatty degeneration. The

tor americanus. The female worm deposits eggs in the intestines; these are carried outward with the intestinal contents. The developed filariform larvae on contact with the skin of a susceptible host penetrate the dermis. The presence of the worm in the dermis and subcutaneous tissues causes a slight inflammatory process with intense itching—ground itch. The worms penetrate the blood vessels and are carried to the lungs. Here they leave the capillaries and enter the alveolar

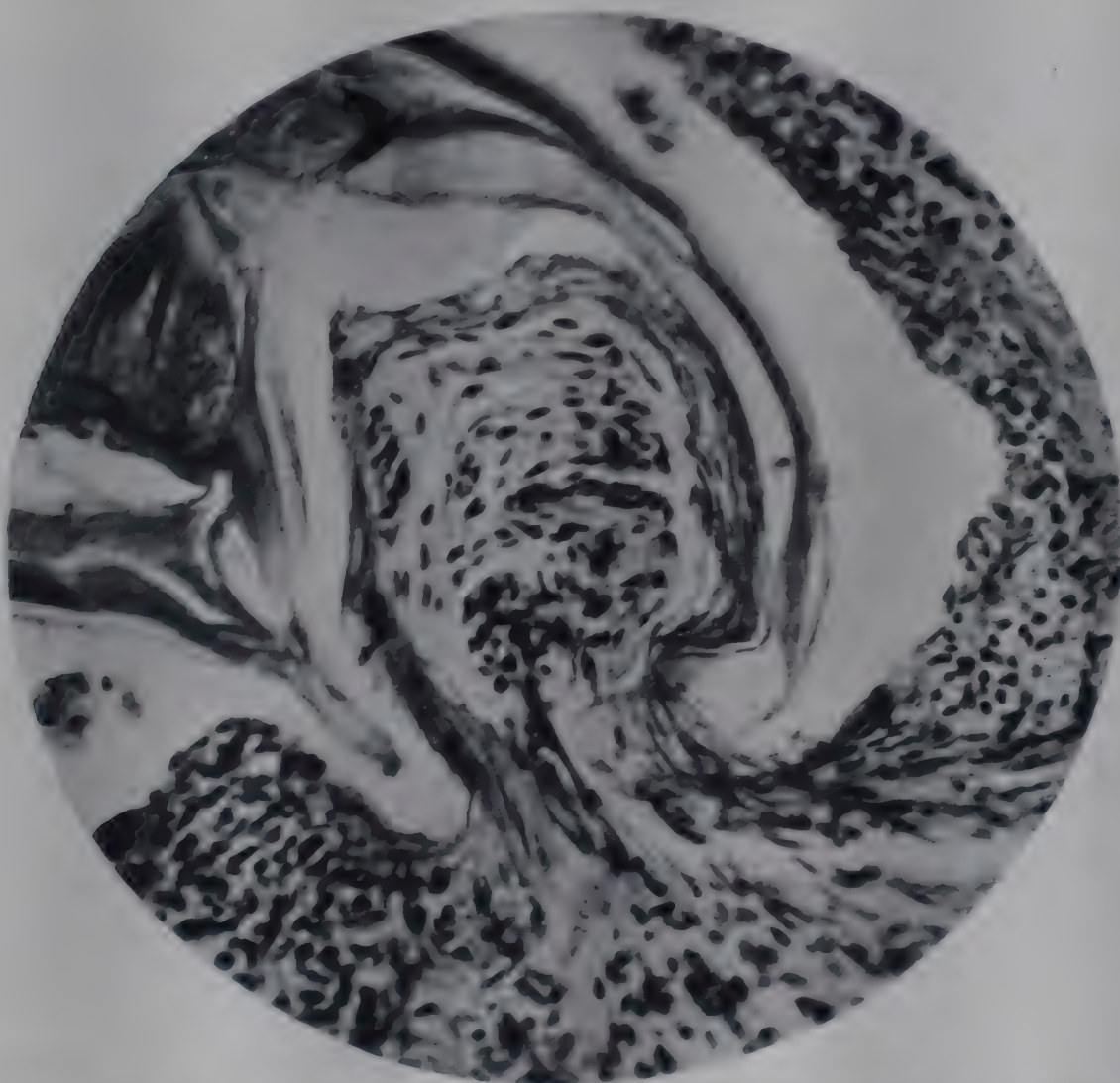


Fig. 238. Hookworm attached to intestinal mucosa. Note submucosa sucked into buccal cavity. (Armed Forces Institute of Pathology, Neg. No. 33819.)

spleen is normal in size or small, and shows an increase of fibrous tissue in the pulp cords. Hemosiderin may be found in the liver and spleen. In some instances the bone marrow is largely replaced by eosinophils and this may account in part for the anemia (Zimmerman). Changes in the other viscera are nonspecific. Lesions of the lungs and skin are found only during the incubation period.

Transmission. There are four species of hookworm which are pathogenic for man: *Ancylostoma duodenale*, *Ancylostoma ceylonicum*, *Ancylostoma braziliense*, and *Neca-*

spaces. There is slight hemorrhage and slight infiltration with lymphocytes and eosinophils into the region. The worms migrate up the trachea and down the esophagus through the stomach into the small intestine to complete the cycle. During the migration through the lungs there may be a rash on the skin, presumably the result of some allergic state. *Ancylostoma braziliense* does not invade the body but migrates about through the subcutaneous tissues bringing about the condition known as "creeping eruption," similar in all respects to cutaneous myiasis.

Incidence. Hookworm disease is found throughout all parts of the world, but is more common in tropical countries where hygienic conditions are poor and there is a greater chance for contamination of the soil. The white man is affected more frequently than the Negro in the proportion of about 4 to 1. Children under five years of age rarely have serious disease, and the greatest peak of incidence is during the second decade of life.

Clinicopathologic Correlation. The presence of worms in the intestine with irritation of the intestinal wall leads to discomfort and pain in the abdomen. The effect on gastrointestinal motility is variable, but constipation is the rule. The anemia—which is the result of three factors: loss of blood by the action of the parasite in the intestine, nutritional deficiency, and defective absorption of food—is probably responsible for the weakness and easy fatigability. Achlorhydria is occasionally associated with the anemia.

Oxyuriasis

Pathologic Anatomy. Pathologic changes resulting from the presence of *Enterobius vermicularis*, or pinworms, are minimal. Catarrhal inflammation and lymphoid hyperplasia have been described, and in not over 5 per cent of patients there is superficial hemorrhage in the appendix, with infiltration with lymphocytes, and necrosis of tissue.

Transmission. Adult worms inhabit the cecum, the appendix, and adjacent portions of the colon and ileum. Females migrate onto the skin about the anus, and discharge their eggs. These eggs are carried by the hands to the mouth, or by fomites to the host or other persons. Swallowed eggs hatch in the duodenum. The larvae liberated pass down the intestine to the cecum, where they mature. *Enterobius* is found throughout the world, but is more common in warmer climates.

Clinicopathologic Correlation. The most prominent clinical symptom of pinworms is the inflammation and pruritus of the perianal skin, caused by migration of the female worms. Within the intestine they produce only a slight inflammation and few clinical signs and symptoms (Miller and Einhorn).

Ascariasis

Pathologic Anatomy. Throughout the United States and in many other parts of

the world infestation with the roundworm, *Ascaris lumbricoides*, is minimal, and the pathologic lesions caused by it are minimal. In most cases there is only slight inflammation of the mucosa. The inflammation is characterized by infiltration with lymphocytes, plasma cells, and eosinophilic leukocytes. There may at times be small superficial ulcerations. Pathologic changes in other viscera are inconspicuous, unless the worms migrate from the intestine.

Transmission. The embryos within the egg in the stool develop in the soil to a vermiform stage and are swallowed by another man or animal. The larvae migrate into the wall of the intestine and are carried by the blood to the liver and to the lungs. In the lungs they set up a mild inflammation with hemorrhage and edema. They migrate from the capillaries into the alveoli, pass up the bronchi and trachea and down the esophagus, through the stomach into the small intestine. Here they establish themselves and develop to mature worms. Occasionally some of the embryos pass through the lungs into the systemic circulation and may be found in the spleen and in many other organs, including the meninges. Ascariasis does not represent the continuation of a single infecting dose but is dependent on continued ingestion of eggs, as is shown by the fact that persons removed from an infested area are spontaneously cured in a few weeks or months. Control of the disease is dependent on control of the pollution of soil by infested persons (Otto and Cort).

Clinicopathologic Correlation. The usual symptoms of ascariasis are abdominal discomfort and disturbed sleep, probably caused by the presence of the worm and its migration into the upper alimentary and respiratory tracts. There is no significant anemia or leukocytes, although there is in most cases a distinct eosinophilia (Keller, Casparis, and Leathers). In general the hilar shadows in roentgenograms are conspicuous in infested persons, and it is possible that they represent the lesions produced by migration through the lung (Keller, Hillstrom, and Gass). It is possible that pulmonary calcification may result from infestation with ascaris (Olson, Wright, and Nolan).

In a rare instance the infestation is heavy, and the mass of worms within the intestine

may produce obstruction of the lumen. Under certain conditions the adult worms may leave the intestine and be found free in the peritoneal cavity, in the bile ducts, and in the lung. There follows a purulent type of inflammation, such as peritonitis or abscess (Ochsner, DeBakey, and Dixon).

Filariasis

Until the 1940's when many American service men lived and fought in the tropics,

and penis in men, and the legs, external genitalia, and breasts in women. The part involved is greatly enlarged. The skin is thickened and hyperkeratotic. The subcutaneous tissues are firm and dense, and are composed of interlacing trabeculae of connective tissue enclosing lobules of edematous fat. The lymphatic vessels are dilated. The adult filarial worm may be found in a dilated lymph vessel or in the lymphoid spaces of the nodes. About the worm there is an organizing fibrinous thrombus occluding the vessel. In the sur-

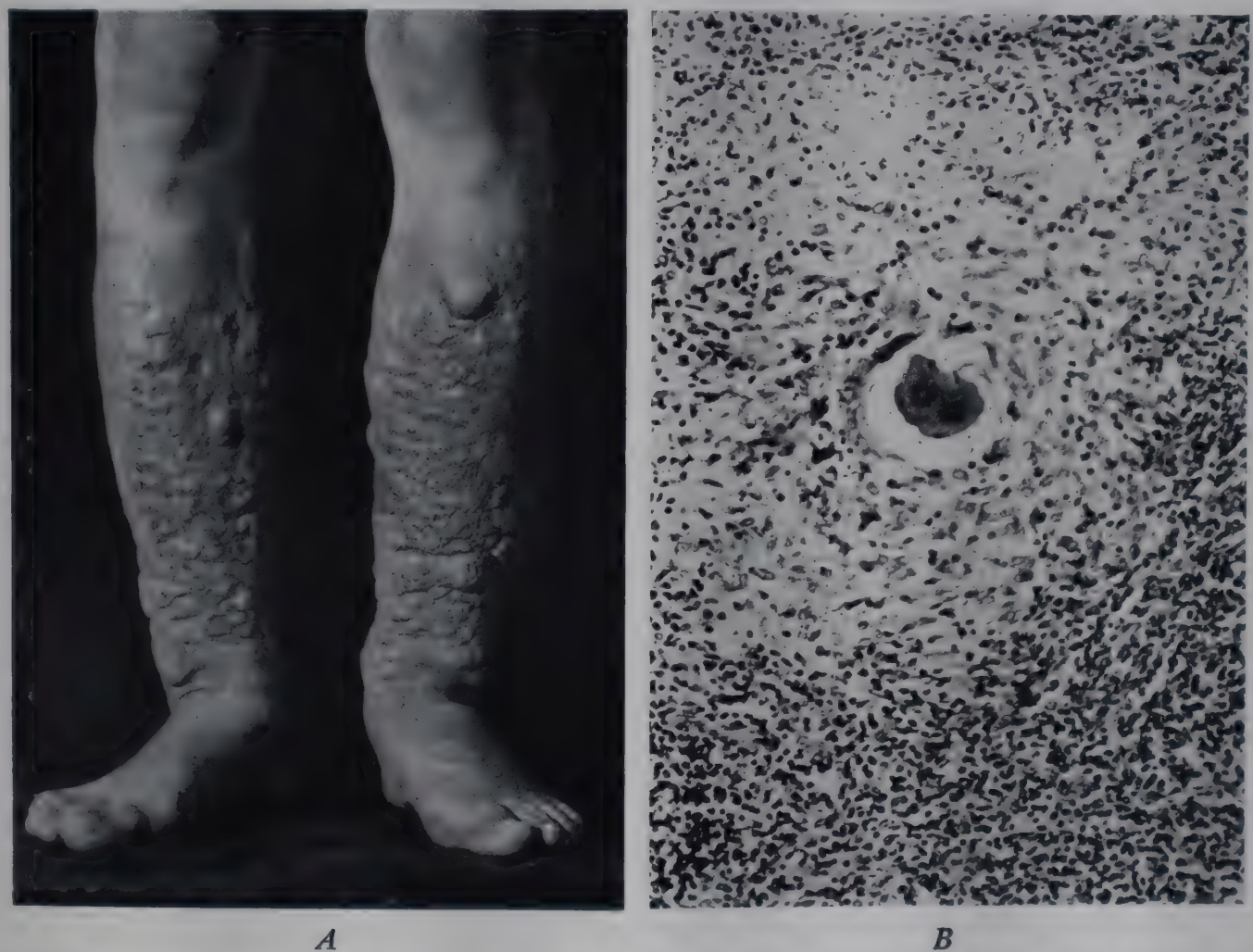


Fig. 239. *A*, Elephantiasis (picture by courtesy of Prof. C. H. Hu). *B*, *Wuchereria* in a lymph node with surrounding epithelioid cells.

filariasis was almost synonymous with elephantiasis. However, it soon became apparent that elephantiasis is a late manifestation of the disease appearing in not over 5 per cent and only after repeated reinfections (Coggeshall).

Pathologic Anatomy. In individuals living in the tropics for short periods or infected only once or a few times, the lymph nodes show a granulomatous inflammation with hyperplasia and tissue eosinophilia. The lymph vessels reveal endothelial hyperplasia and thrombi. Adult worms may be observed in the sections (Wartman; Michael).

Elephantiasis involves the legs, scrotum,

rounding tissue there are fibrosis and cellular infiltration with lymphocytes, eosinophils, and plasma cells. Dead worms may be surrounded by giant cells or may calcify.

Transmission. The adult worms are encysted in the lymphatic vessels, usually of the lower extremities. In most parts of the world, the Pacific islands excepted, the microfilaria, representing the next generation, migrate into the peripheral blood stream at night only. Mosquitoes of the genera *Culex*, *Aedes*, and *Anopheles*, feeding on infected patients, take up some of the microfilaria. After a week or ten days filariform larvae are ready to be introduced by the sting of this animal into a new

human host. *Wuchereria bancrofti* is found in all parts of the world in a band extending several degrees on both sides of the equator.

Clinicopathologic Correlation. Many pa-

swelling, and redness. The late change, elephantiasis, results from obstruction of the lymphatics by the worms and the fibrous tissue incident to their presence.

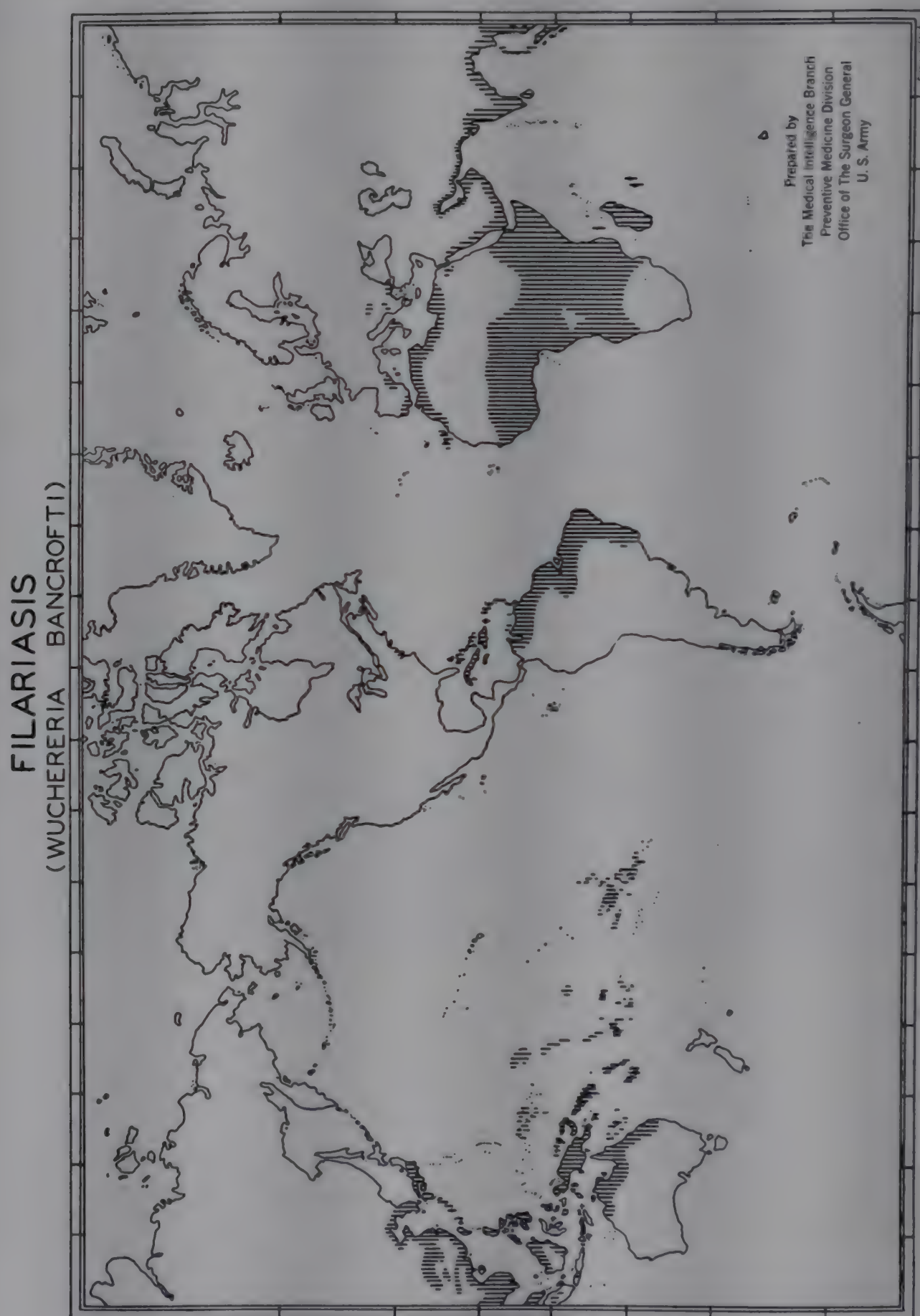


Fig. 240. Worldwide distribution of filariasis.

tients with filariasis have no signs or symptoms. Following the bite of an infected mosquito there is an incubation period of at least three months. On localization of the adult worms in the lymphatics there is an acute inflammation characterized by local pain,

Dracunculiasis

The worm, *Dracunculus medinensis*, is known as the guinea worm. It is common in Egypt, the Near East, India, and in the southern part of Soviet Russia. The appearance of

a small papule, usually on the sole of the foot, marks the onset. This rapidly changes to a blister which ruptures, and a single large guinea worm protrudes. If the person with this lesion wades in water, motile larvae are ejected by the female worm, and ingested by snails of the genus *Cyclops*. Man is infected by ingesting water contaminated with *Cyclops*. In man the larvae develop, invade the wall of the intestine, and for a period of eight to twelve months migrate through the tissues and finally arrive at the subcutaneous tissue of the foot, completing the cycle (Macfie).

Schistosomiasis

There are three important species of *Schistosomatoides* producing disease in man: (1) *Schistosoma haematobium*, causing urinary schistosomiasis or bilharziasis; (2) *Schistosoma mansoni*, causing Manson's intestinal schistosomiasis; and (3) *Schistosoma japonicum*, causing oriental schistosomiasis.

General Pathologic Anatomy. Under ordinary conditions *Schistosoma* in the cercarial stage enters the skin of the lower extremities from infected water, and the larvae by direct motion and by lysis gain entrance to the lumens of small veins. There are small hemorrhages in the dermis, but little inflammation. The larvae pass through the lung and are carried into the systemic circulation. There have been no histologic studies in man of the reaction in the lung, but in animals there is an intense inflammation (Faust, Jones, and Hoffman). The larvae do not survive in any organs except those supplied by the mesenteric arteries. In the mesenteric region they pass through the capillaries and are carried in the portal circulation to the liver. In this organ the larvae develop, differentiate sexually, and on reaching maturity move out of the liver against the current of blood in the portal vein. During intravenous migration, or on arrival in the tissues of the intestine, mesentery, peritoneum, or bladder, the worms mate, and the fertile females begin to lay eggs.

The three species show quantitative differences in the site of final migration. *Schistosoma haematobium* is predominantly in the bladder and the rectum; *Schistosoma mansoni* in the colon and liver; and *Schistosoma japonicum* in the small intestine, colon, and liver.

Schistosomiasis of the Bladder and the Intestine. The adult female worms lay eggs within the small venules of all layers of the affected hollow viscus, and the embryos break through the wall of the venule and come to lie free in the tissues. There are an intense edema, hyperemia, and infiltration with polymorphonuclear leukocytes, eosinophils, lymphocytes, and mononuclear cells. The entire area may undergo necrosis and ulcerate into the lumen. In the deeper tissues the eggs cannot be extruded and they cause proliferation of connective tissue and later die. Foreign body giant cells surround the dead eggs and in some instances they become calcified. Similar lesions are found in the mesentery, peritoneum, and in the mesenteric lymph nodes. In women the mucosa of the vagina and the uterus on occasion become infected. In late stages there is extreme hyperplasia of the mucosa, and not infrequently neoplastic proliferation to form polyps or carcinomas of the bladder and colon. Secondary bacterial infection may lead to the formation of fistulous tracts (Hutchinson; Giffen).

Schistosomal Cirrhosis. The liver is normal or increased in size and averages 1800 gm. in weight. Through the surface may be seen a network of broad, white, interlacing trabeculae. In the capsule there are small, white, firm nodules, 1 to 3 mm. in diameter. On section there is the same network of white, firm tissue. There is no lobulation of the hepatic parenchyma (Fig. 254, B) such as is seen in ordinary cirrhosis. Microscopically abundant connective tissue is seen in the larger portal spaces, infiltrated with leukocytes, eosinophils, and mononuclear cells. The larvae, both dead and alive, are embedded in the connective tissue (Symmers; Faust and Meleney).

It is thought that schistosomal cirrhosis represents a reinfection. The eggs deposited in the bladder and intestine, instead of rupturing into the lumen and leaving the body, enter the branches of the portal vein, and are swept upward into the intrahepatic radicles.

Life Cycle. The eggs and larvae leave the body in the urine or feces. The developed miracidia on contact with the proper species of snails produce cercarial forms which leave the snail. These enter the skin of man or animals who wade in infected water.

Incidence. *Schistosoma haematobium* is

endemic in the Nile Valley and in other parts of Africa. In the delta of the Nile over 50 per cent of the population are infected, and 10 to 20 per cent of all deaths result directly from schistosomiasis. *Schistosoma mansoni* is

Valley. *Schistosoma haematobium* and *Schistosoma mansoni* have been observed only in man and monkeys. *Schistosoma japonicum* produces natural disease in man, dogs, cats, rats, mice, cattle, and horses.

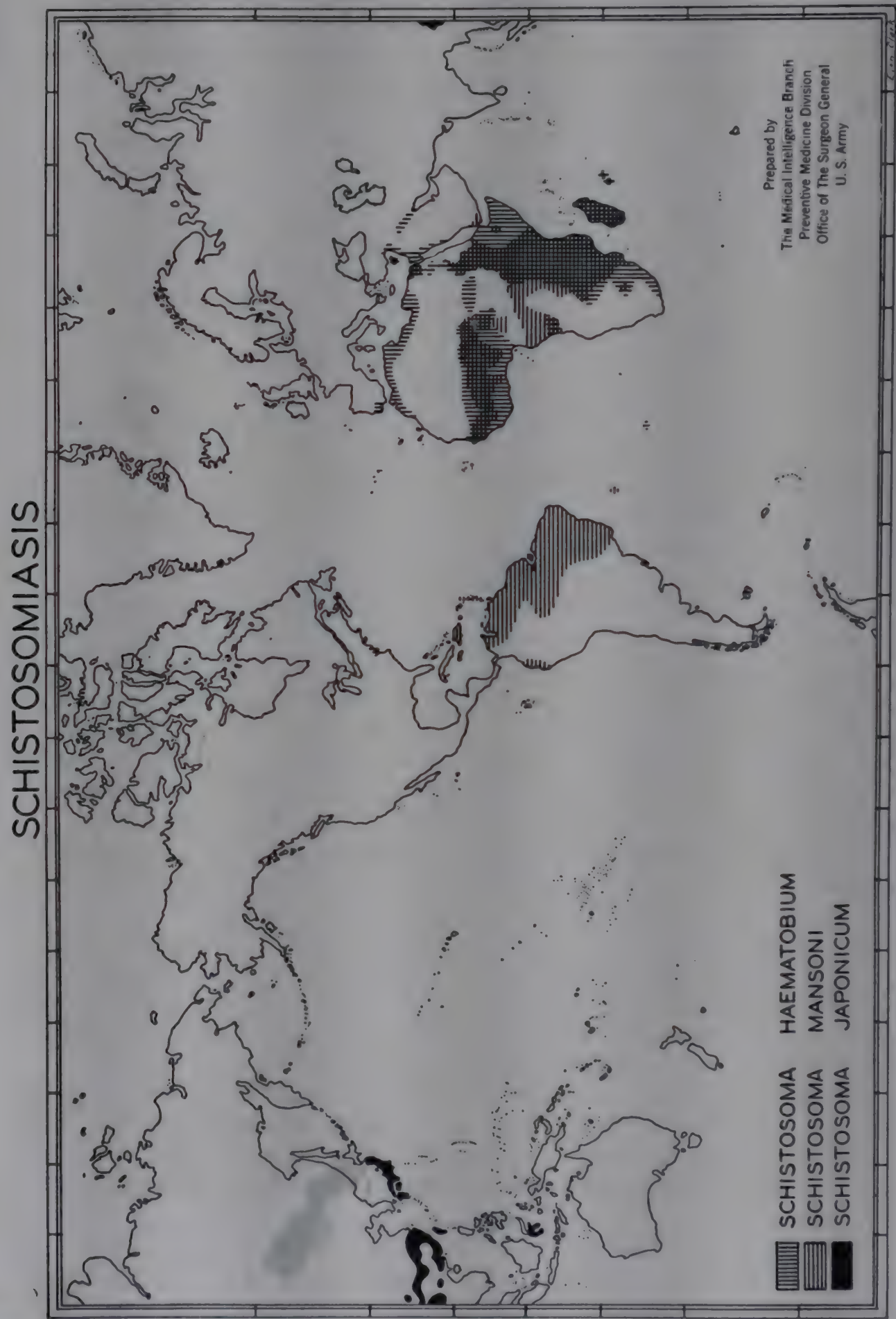


Fig. 241. Worldwide distribution of the three types of schistosomiasis.

found in Africa, northern Brazil, Venezuela, Dutch Guiana, and the Lesser Antilles. *Schistosoma japonicum* is endemic throughout Japan and China, especially in the Yangtse

Clinicopathologic Correlation. The clinical course of the disease in man is usually divided into three stages. Following penetration of the skin there is a long incubation period of

about a month, during which time the larvae enter the portal circulation. There follows a period of one to three months of invasion of the mesenteric area. During this time the in-

The eggs may be readily demonstrated in these same fluids. The third stage results from the fibrosis and hyperplasia. In the bladder there is obstruction at the internal orifice and

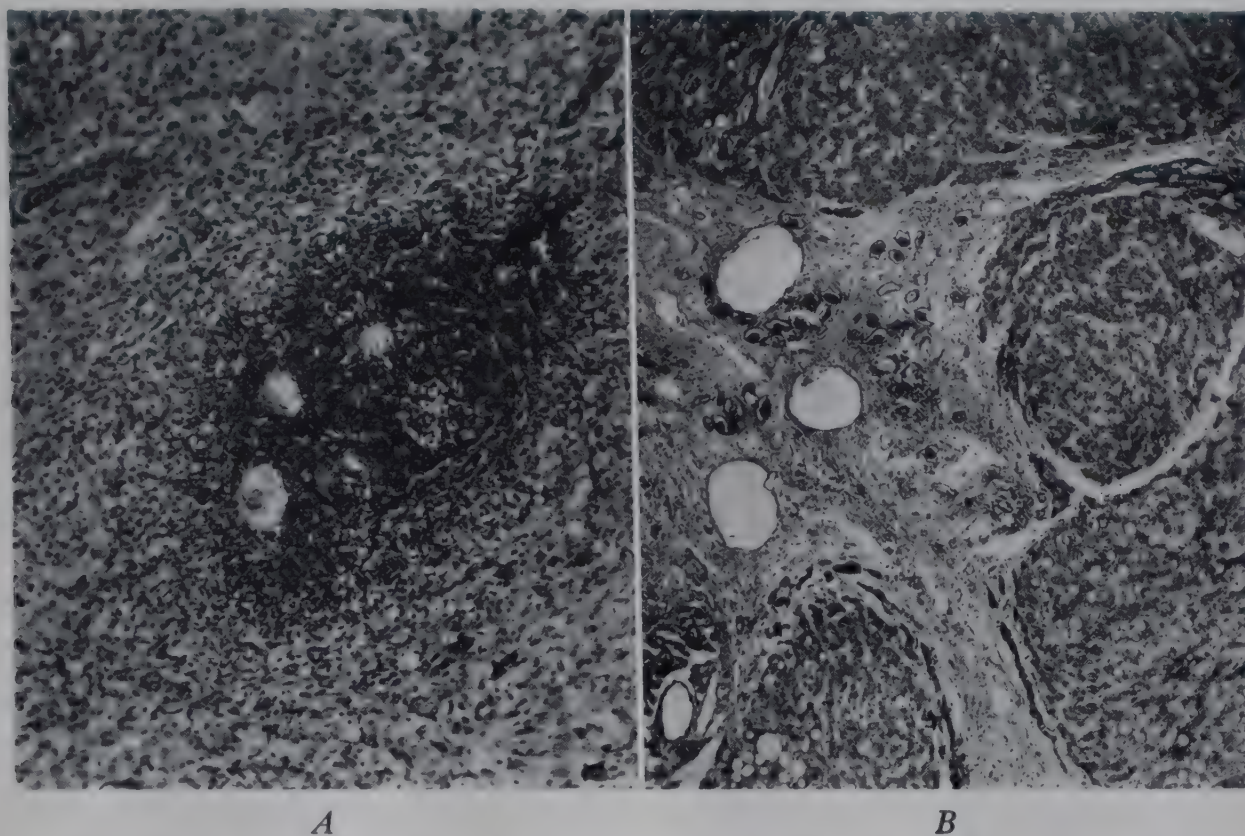


Fig. 242. Schistosomiasis of liver. *A*, Early lesion with necrosis and cellular infiltration. *B*, Late lesion with calcified ova and cirrhosis. (Tissue by courtesy of Armed Forces Institute of Pathology, Acc. No. 60827.)

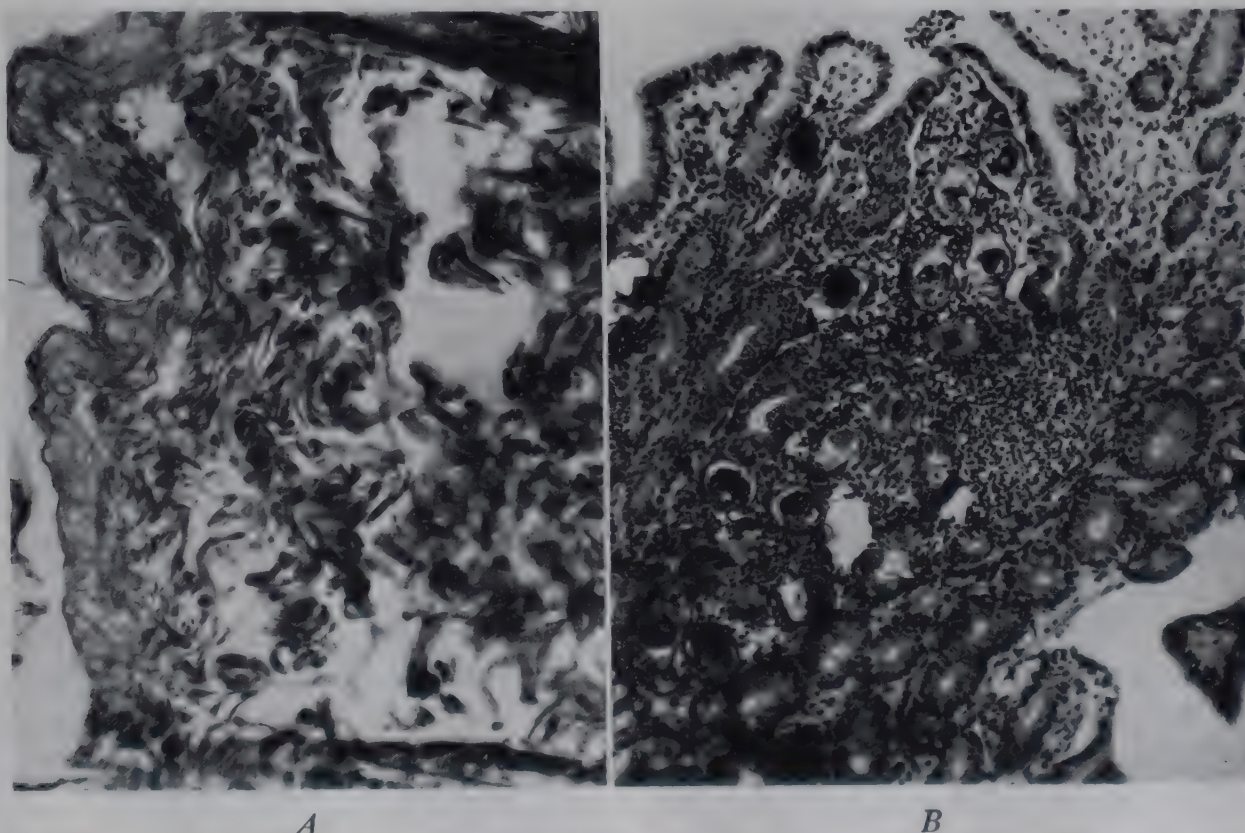


Fig. 243. *A*, Schistosomal cercaria penetrating skin. *B*, Experimental schistosomiasis of the colon. (Tissue by courtesy of Dr. H. Tsuchiya.)

flammation may be reflected by systemic changes, such as fever, general malaise, diarrhea, and anorexia. The ulceration into the lumens of the hollow viscera results in the presence of blood in the urine or feces.

scarring of the wall of the bladder. In the colon there is obstruction, resulting from cicatricial contracture or from large polyps or carcinomas. In the liver the cirrhosis leads to advanced obstruction of the portal circulation,

with all of the changes of passive hyperemia in this region, notably ascites. Complement-fixation tests and skin reactions using an antigen made from the powdered liver of infected snails have been found useful in diagnosis (Taliaferro and Taliaferro). There is a systemic eosinophilia as well as infiltration of eosinophils into the tissues.

Schistosomal or Cercarial Dermatitis. In certain parts of Michigan, New Zealand, and South Africa varied strains of cercaria may invade the skin of man and produce an erythematous macular or papular eruption. There

Pulmonary Distomiasis. The most important species is *Paragonimus westermani*. The adult worm encapsulates in a cyst in the lung, filled with a thick fluid; eggs escape into the bronchi and are coughed up and ejected in the sputum, or swallowed and passed in the feces. After passage through two intermediate hosts, snails and crayfish or crabs, it returns to man in ingested raw meat of the second intermediate host and passes through the intestinal wall, the peritoneal cavity, the diaphragm, and the pleural cavity to the lung. In the lung there are an exudate of polymor-

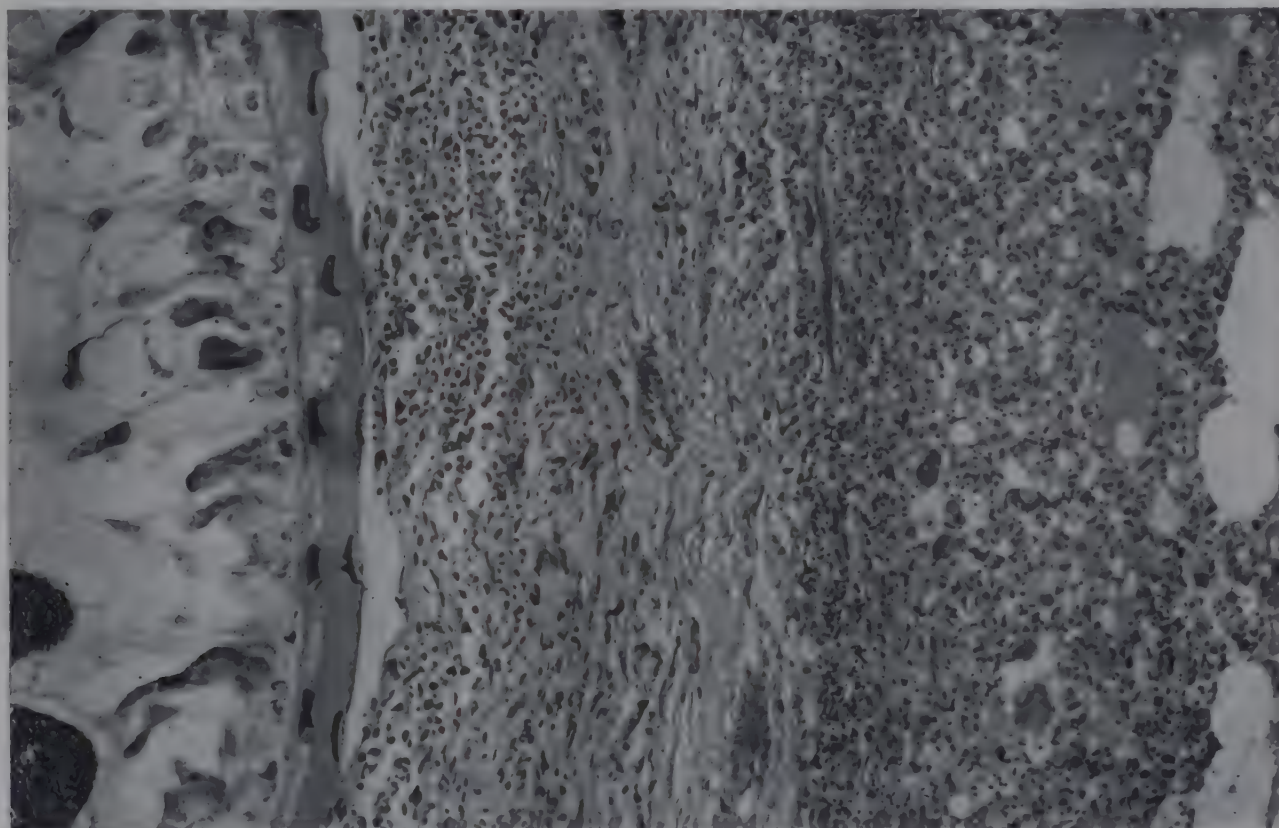


Fig. 244. Wall of a pulmonary cyst of *Paragonimus westermani*. (Armed Forces Institute of Pathology, Neg. No. 74379.)

is no further invasion of the body (MacFarlane).

Distomiasis

Distomiasis in man may be produced by the presence of the parasite in the intestine, liver, or lung.

Intestinal Distomiasis. The more important species are *Fasciolopsis buski*, edemic in the Orient; *Heterophyes heterophyes*, in the Nile delta, and the Orient (Bey); and *Metagonimus yokogawai*, in Soviet Russia. The adult worm attaches to the mucosa of the duodenum or jejunum. There are hemorrhage, ulceration, and infiltration of the mucosa with polymorphonuclear leukocytes, eosinophils, and lymphocytes.

phonuclear leukocytes and eosinophils, and encapsulation by fibrous tissue. Rarely cysts are found in other organs.

Hepatic Distomiasis. Most important of the liver flukes producing disease in man are: *Fasciola hepatica* (sheep liver fluke), prevalent in all sheep-raising countries; *Opisthorchis felinus* (cat liver fluke), a common fluke in man in Russia and Siberia; and *Clonorchis sinensis* (Chinese liver fluke), causing clonorchiasis in Japan, China, and Indo-China. The adult worms are within the intrahepatic branches of the bile ducts, and less commonly in the pancreatic ducts. There is hyperplasia of the biliary epithelium, infiltration with lymphocytes and eosinophils, and fibrosis in the periductal tissues. The eggs leave the body with the feces. After further development they

invade certain species of snails, and mature to cercaria. The free-swimming cercaria of the Chinese and the cat liver fluke then invade the muscles of fish, and ingestion of the meat of the fish by man brings the parasite back to the duodenum. The cercaria of the sheep liver fluke encyst on moist vegetation, and this is then ingested by the definitive host. In the duodenum the worms mature and ascend the ducts to complete the cyst.

Salmon Poisoning. Salmon poisoning in dogs and other animals of the Pacific Northwest and Siberia apparently results from the ingestion of raw salmon containing the worm, *Troglotrema salmincola*, which in turn harbors a virus that is the true cause of the disease (Witenberg).

Diphyllobothriasis

Infestation with *Diphyllobothrium latum* is associated with a condition clinically indistinguishable from pernicious anemia.

Pathologic Anatomy. In carriers of the worm who do not have an anemia there are usually no pathologic changes, but some patients without evident anemia have an acute or chronic type of atrophic glossitis. Clinically there are vague nervous and gastrointestinal disturbances, but no related anatomic changes are found at autopsy. The head of the worm is usually attached in the middle part of the ileum.

In patients with anemia, the pathologic changes are identical with those in pernicious anemia. There are megaloblastic hyperplasia of the bone marrow, hemosiderosis of the liver and spleen, hypertrophy and dilatation of the heart, fatty degeneration of the heart, and in an occasional case subacute combined disease of the spinal cord.

Transmission. Ova leaving the gastrointestinal tract of man are consumed by certain crustaceans, in which they develop into a proceroid stage in about three weeks. The crustaceans are eaten by fish, and the fish, improperly cooked or preserved, are eaten by man, and the cycle is completed.

Geographical Distribution. The broad fish tapeworm is found in all parts of the world except Australia. There are two important foci: the Baltic states (especially Finland) and Japan. In some parts of Finland 100 per cent of persons are infested. Several species

of fish in the freshwater lakes of North America are infested, and it is probable that the broad fish tapeworm is the organism in over one-half of the infestations of man with cestodes in the north central United States and central Canada.

Teniasis. Hymenolepiasis

There are three important cyclophyllidean tapeworms for which man is the definitive host. *Taenia solium* is most common in the Balkan states of Europe, *Taenia saginata* in the Mohammedan countries, North Africa, and the Near East, and *Hymenolepis nana* in Europe and the United States. It is estimated that *Hymenolepis nana* is the cause of over 90 per cent of all tapeworm disease in the United States, and that from 1 to 2 per cent of the population of the southern United States is infested with this helminth.

Pathologic Anatomy. Pathologic changes directly attributable to the tapeworm are inconspicuous. Occasionally there are petechiae or minute ulcers at the point of attachment of the scolex. Rarely a mass of worms may obstruct the intestine, or a proglottid may occlude the lumen of the appendix. An infrequent complication is perforation of the intestine by a scolex, with resulting peritonitis.

Transmission. Human infection with *Taenia solium* and *Taenia saginata* is acquired by the ingestion of the meat of the hog and of the cow respectively, which is infested with cysticerci of these tapeworms. *Hymenolepis nana* is passed from man to man directly, with the rat and mouse serving as reservoirs.

Clinicopathologic Correlation. There is little correlation between the usual signs and symptoms of teniasis—abdominal discomfort, ravenous appetite, nervousness, etc.—and the anatomic lesions. It is possible that toxic substances are elaborated by the worms and absorbed. Prognosis in teniasis *solium* is less favorable because of the possible self-reinfection and development of cysticerciasis.

Cysticerciasis

Pathologic Anatomy. If man ingests eggs of *Taenia solium* contained in human intestinal content, or if mature proglottids are forced into the stomach by reverse peristalsis, the embryos are liberated by the action of

gastric juice. The larvae tapeworm, known as *Cysticercus cellulosae*, invades the intestine, enters the blood, and is distributed to all of the tissues of the body. Full development takes place in the subcutaneous tissue, brain, orbit, musculature, heart, liver, lungs, and peritoneum, with the formation of a cyst. Each cyst consists of a clear, translucent membrane, with an opaque white spot at one point, representing the worm. Microscopically a surrounding fibrous capsule is seen, infiltrated with eosinophils and polymorphonuclear leu-

regions where personal hygiene is at a low level.

Echinococcosis

Pathologic Anatomy. The typical pathologic change in echinococcosis is the formation of a cyst or cysts in the viscera or other tissues. After lodgment of the embryo in a capillary there is an inflammatory reaction with infiltration with monocytes and eosinophils. Many embryos are thus destroyed, while others sur-

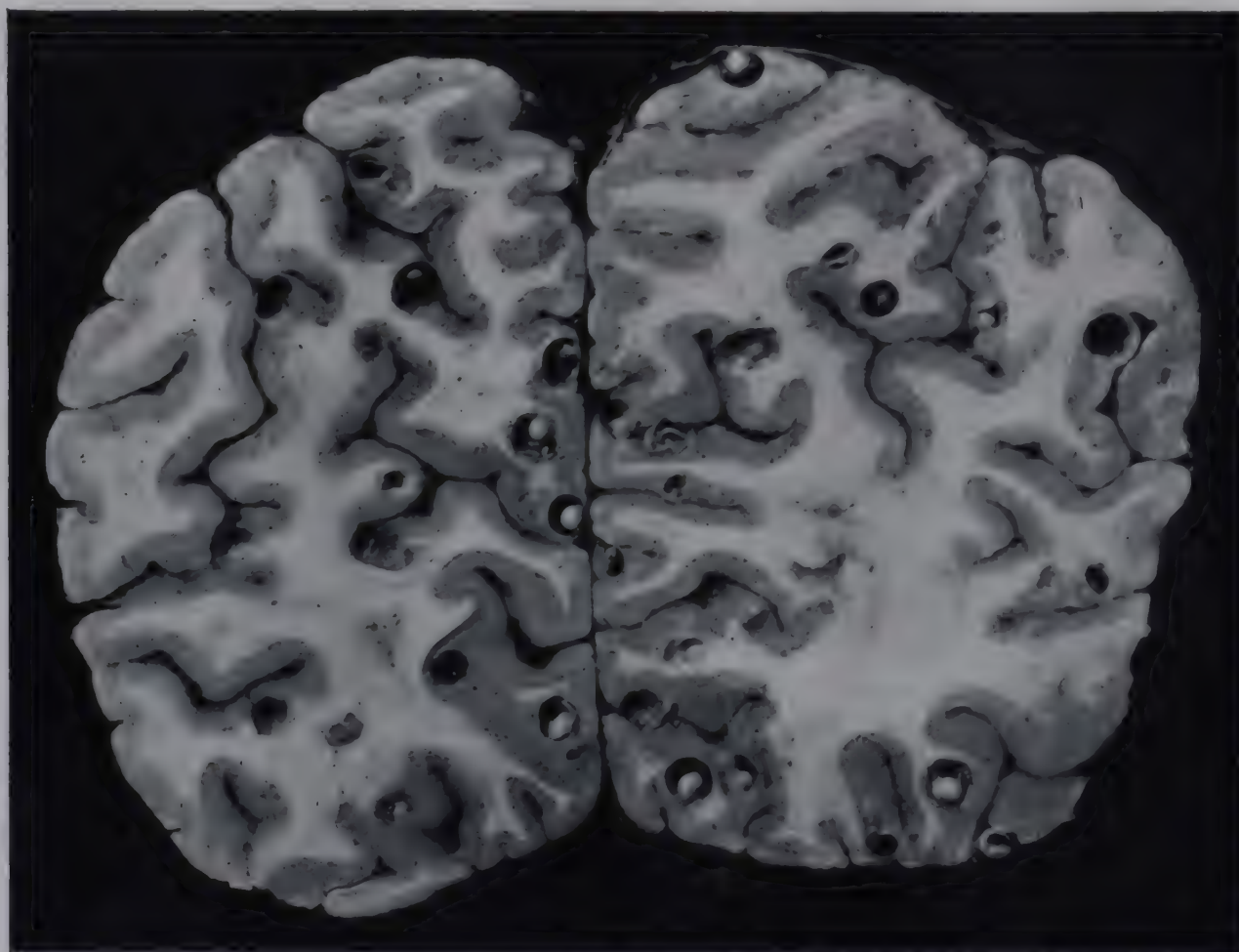


Fig. 245. Cysticerciasis of the brain. (Photograph by courtesy of Prof. C. H. Hu.)

kocytes. After several months or years many of the worms die, and there is a conspicuous reaction, with necrosis of the worm and some of the surrounding tissue, infiltration with eosinophils and polymorphonuclear leukocytes, formation of giant cells, and eventually calcification (Ch'in).

Clinicopathologic Correlation. The cysts produce symptoms almost entirely because of the pressure on surrounding structures. Many instances of epilepsy are believed to be caused by a cysticerciasis of the brain (Chung and Lee; MacArthur). A precipitin test and an intradermal reaction, group-specific for all cysticerci, may be useful in diagnosis. Cysticerciasis is found in all parts of the world where *Taenia solium* is found, but especially in those

vive and continue to develop. By the end of the third week the cyst has attained a diameter of 250 microns. About the cyst wall there are epithelioid cells, giant cells, and eosinophils, in turn surrounded by an outer layer of fibroblasts infiltrated with eosinophils. By the fifth month the cyst is 1 cm. in diameter and the intrinsic wall may be clearly separated into two parts: an outer, opaque, non-nucleated layer, and an inner, nucleated, germinal layer. Numerous small brood capsules project into the cavity from the inner layer. From the inner wall of these capsules the scolices develop and invaginate so that the rostellar hooklets are embedded. If the cyst ruptures at one point, the scolices are forced into the surrounding tissue and daughter cysts develop. In bone the

growth of the cyst is retarded by the thick cortical bone, and there is not full development as described above (Fairley). In cer-

daughter and granddaughter cysts continue to grow in the same organs, or are carried by the blood as metastases.

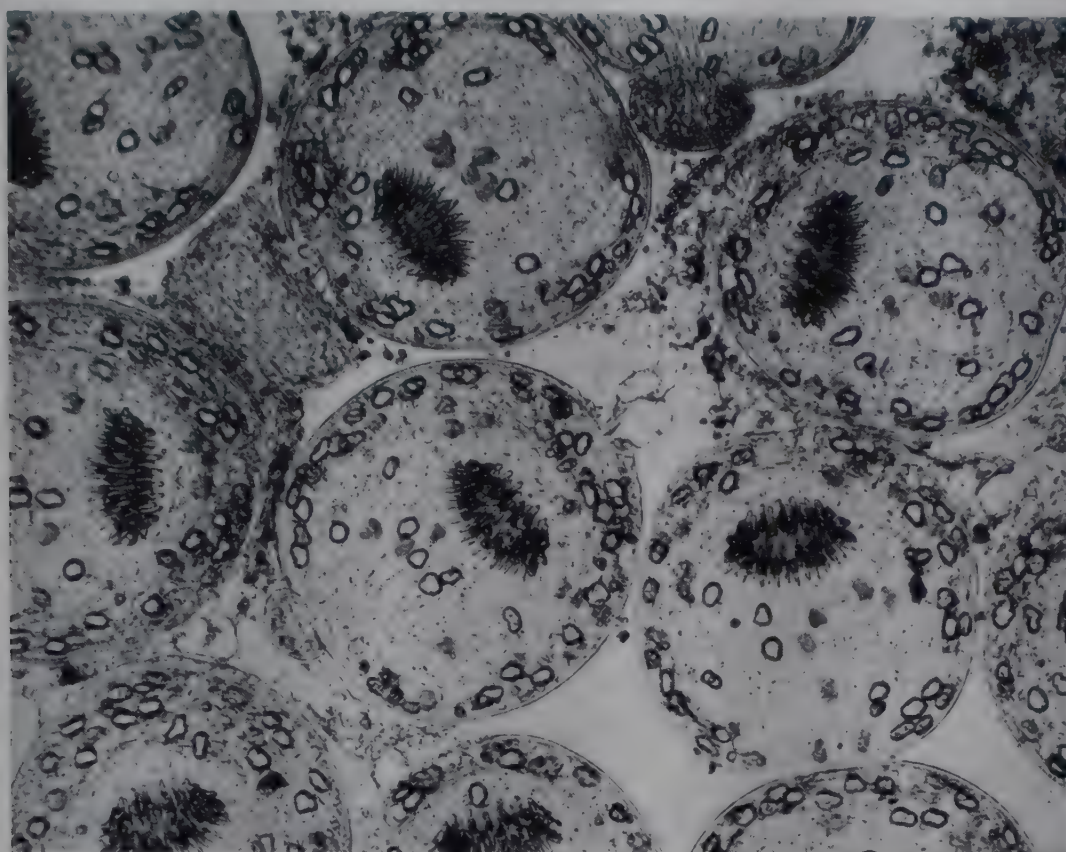


Fig. 246. *Echinococcus*. (From a negative taken by the late Dr. Howard A. McCordock.)

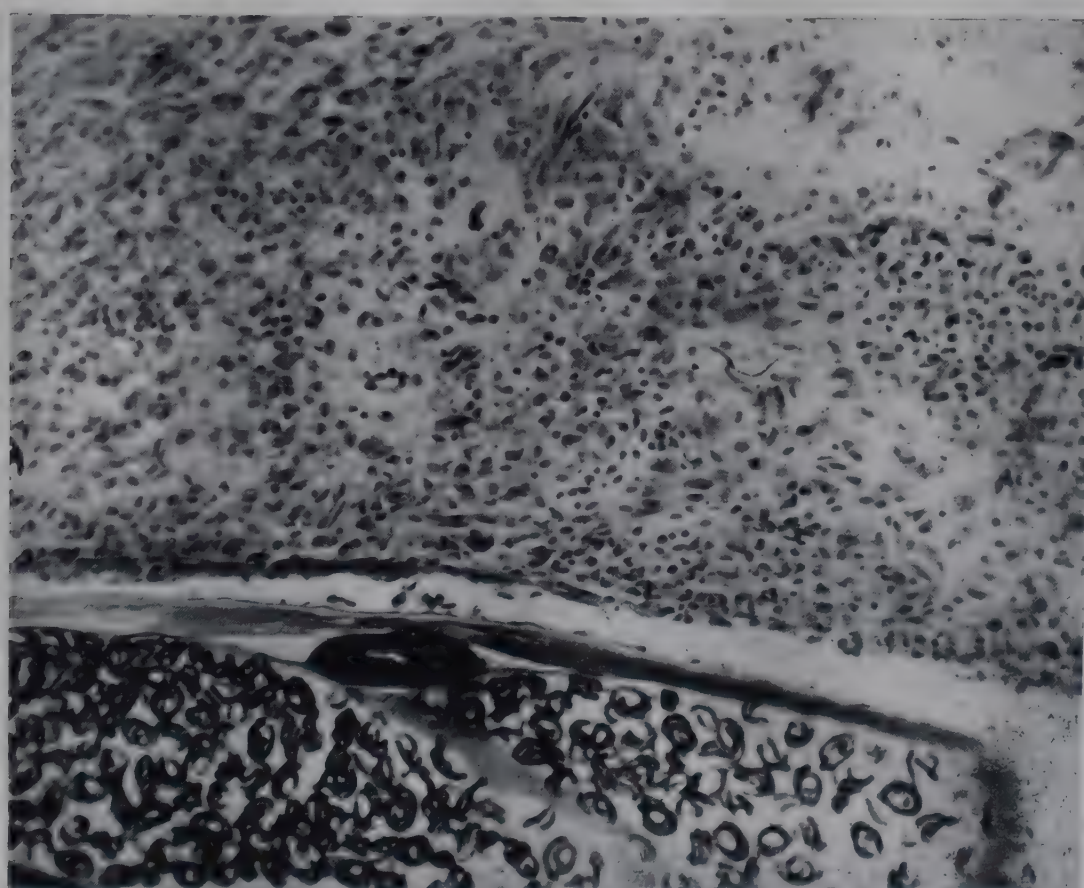


Fig. 247. *Onchocerciasis*. (Tissue by courtesy of Dr. Russell Blattner.)

tain parts of the world, notably western Germany and the surrounding Alpine country, and in eastern Russia and western Siberia, another type of hydatid develops in man, known as the alveolar hydatid. Germinal tissue breaks through the outer laminated membrane and

Incidence. Hydatid disease is most common in the great sheep and cattle raising regions of the earth—Iceland, New Zealand, Australia, Argentina, the northern and southern tips of Africa, in a belt across Europe and central Asia, and in the United States.

Transmission. The reservoir of *Echinococcus granulosus* is sheep, cattle, and pigs, and to a less extent horses, camels, goats, and other mammals. The flesh of these animals is eaten by the dog, wolf, jackal, and cat. Contamination of human food and drink by the offal of these latter is responsible for the disease in man.

Clinicopathologic Correlation. The cysts grow slowly and patients who acquire the infection during childhood or young adulthood rarely present themselves to a physician before middle life. The clinical changes are dependent on pressure of the enlarging cyst on surrounding structures. There is an eosinophilia of from 10 to 25 per cent in the peripheral blood. Patients occasionally have severe anaphylaxis on rupture of the cyst. The only known treatment is surgical removal, but this is difficult because soilage of the surrounding tissue only serves to reestablish the disease (Magath).

Onchocerciasis

The worm, *Onchocerca volvulus*, encysts in the subcutaneous tissues and forms small firm nodules on any part of the body, but most commonly about the great joints and in the temporal and occipital regions of the scalp (Goldman). On section there is a fibrous capsule enclosing a softer cavernous tissue, within which the adult worms and the microfilaria are found. Occasionally the tissues of the orbit are involved, with secondary changes and atrophy of the optic nerve (Silva). The condition is endemic in Africa, Guatemala, and southern Mexico. The life cycle is similar to that of *Wuchereria*. The black gnat (*Simulium*) is the intermediate host (Blacklock). The prognosis is good if the eye is not involved.

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LVI

Diseases Caused by Arthropods

Arthropods are important not so much in causing human disease as in the biological transmission to man of bacteria, viruses, rickettsia, and protozoa. Mention of only a few of these will serve to emphasize this statement: the transmission of malaria, a protozoan disease, by the mosquito; the transmission of plague, a bacterial disease, by the flea; the transmission of typhus fever, a rickettsial disease, by the louse; and the transmission of yellow fever, a viral disease, by the mosquito. In each of these cases the transmission is truly biological: the parasite is ingested by the insect, and after a certain period the disease-producing agent may be transmitted to another human being. In addition, certain other arthropods serve as mechanical vectors of important diseases, such as salmonellosis, bacillary dysentery, and amebic dysentery.

In a few instances the arthropod causes disease directly, which will be discussed in this chapter.

Arachnidism

Arachnidism is the characteristic clinical syndrome which follows the bite of a spider: excruciating pain progressing toward the trunk, followed by intense pain in the thorax and abdomen, and the signs and symptoms of shock. In almost all cases there is, within a period of twelve to twenty-four hours, complete recovery, but in the occasional person who dies, there are few pathologic changes. The viscera are hyperemic and the lungs are edematous. In the United States the only proved poisonous spider is *Latrodectus mactans*, popularly known as the Black Widow spider. In the South one of the most common sites for bites is on the scrotum, from spiders in the outhouses (Blair).

Tick Paralysis

Rarely following the bite of a tick of the genus *Dermacentor* a peculiar paralysis sets in on the sixth to the eighth day. The mortality varies from a few per cent to as high as 20 per cent. At autopsy there are no significant pathologic changes. Prompt removal of the tick, even after the onset of paralysis, brings about cure. No virus or bacterium can be isolated (Robinow and Carroll).

Diseases Caused by Mites

There are two important superfamilies of mites responsible for disease in man: (1) the sarcoptoid, itch, or mange mites (*Sarcoptoidea*) producing scabies; and (2) harvest mites (*Trombidoidea*) responsible for the condition known as chiggers. Less important are the follicular mites (*Demodicoidea*) (Ayres and Anderson); the parasitoid mites (*Parasitoidea*), including the rat mite, a vector of endemic typhus (Dove and Shelmire); and the predacious or grain mites, producing dermal lesions in threshers and in those working about grain and straw.

Scabies. The cause of scabies is the mite, *Sarcoptes scabiei*. These mites live in cutaneous burrows and the female deposits eggs over them. The eggs hatch, and six-legged larvae emerge. These produce lateral tunnels or escape onto the surface and invade new hair follicles. About the burrows there is slight fibrosis and infiltration with lymphocytes and eosinophilic leukocytes. There is an eosinophilia of the blood, varying from 5 to 15 per cent. As the mites feed on the tissue, minute fecal pellets are deposited, and it is believed that these are responsible for the edema of the dermis and vesicle formation in the epidermis. Norwegian scabies is caused by another

variety, *Sarcoptes scabiei crustosae*. In this disease there is extensive ulceration and crusting of the skin.

Chiggers. There are three important species of chiggers or red bugs: *Trombidium irritans* of North America, *Trombidium autumnale* of Europe, and *Trombidium akamushi* of Japan. The eggs hatch on the ground, and six-legged larvae attach themselves to vegetation. As man or animals walk through this vegetation the larvae attach to the skin. A small macule appears which is characterized by

manus corporis, and *Phthirus pubis*, known as the head louse, the body louse, and the crab louse, respectively.

Pathologic Anatomy. Lesions are produced on the skin by either nymph or adults as the result of feeding. Saliva produced in the reniform salivary glands is introduced into the puncture wound, and there develops within a few hours a roseate elevated papule. Microscopically hemorrhage into the tissues, edema, and infiltration with lymphocytes are seen. After several days the changes are largely the



Fig. 248. Scabies of hands. (Armed Forces Institute of Pathology, Neg. No. 73527.)

edema, hyperemia, and infiltration with lymphocytes and eosinophils. The irritating action is the result of the secretion of the salivary glands of the larvae. The larvae, engorged with blood, drop to the ground, become nymphs, and mature. Some people are extremely sensitive to chiggers and suffer from systemic symptoms, with fever and urticaria. In Japan and in the southern Orient the mite is the vector of tsutsugamushi disease and of scrub typhus.

Pediculosis

Pediculosis is infestation with lice. It is most common wherever personal hygiene is poor. Lice infesting man are of three types: *Pediculus humanus capitis*, *Pediculus hu-*

manus corporis, and *Phthirus pubis*, known as the head louse, the body louse, and the crab louse, respectively. After long-continued infestation with lice, particularly with the crab louse, there is pigmentation of the skin, resulting from both the hemorrhage of primary injury and the scratching.

Myiasis

Myiasis is the invasion of the tissues by the larvae of flies. According to the location, it is designated as cutaneous (Montgomery), ophthalmic (Anderson), nasal, aural (Plott and Scott), laryngeal (Miller), or vulvar myiasis. In the subcutaneous tissues the larvae may move about, producing one variety of the clinical condition known as creeping

eruption. Eggs of some of the flies may be deposited on food, which is then eaten, and the larvae attach in the folds of the stomach or intestine, producing an intestinal myiasis (Herms and Gilbert; Causey). In all types of myiasis children are more frequently affected than adults.

Pathologic Anatomy. The reaction of the tissues consists of slight edema and hyper-

Chigoes. The female of the jigger flea, *Tunga penetrans*, burrows into the skin of the feet and ankles. The presence of the organism sets up a mild inflammatory process characterized by edema and hyperemia, resulting in intense itching. If the infestation is severe, ulcers develop, and these are a serious problem among the barefooted peoples in Africa (Gordon).



Fig. 249. Myiasis—creeping eruption of botfly. (Armed Forces Institute of Pathology, No. 48282.)

emia, and infiltration with polymorphonuclear leukocytes, eosinophils, and plasma cells. In the dermis there may be small foci of necrosis, and in the epidermis there is slight acanthosis, edema, and vesicle formation (Montgomery).

Diseases Caused by Fleas

The flea is the biological vector of plague, typhus fever, and tularemia.

The bite of a disease-free flea causes little inconvenience. There is a local area of inflammation, appearing grossly as a roseate, raised, edematous lesion. Microscopically edema and hyperemia and infiltration with lymphocytes are seen. Secondary infection from scratching may ensue.

Vesication, Urtication, and Venenation Caused by Insects

A wide variety of insects may cause either local or systemic manifestations as the result of a bite or of contact. The more important of these are the beetles; moths and butterflies; bees, wasps, and hornets; bedbugs; and mosquitoes.

Pathologic Anatomy. The initial reaction to an insect bite is congestion and edema. If the reaction persists there are hyperplasia of epithelium and infiltration with eosinophils and plasma cells (Allen).

Beetles (Coleoptera). Blister beetles of the family Meloidae contain cantharidin, most concentrated about the genital apparatus

(Hinman). The lesion produced by crushing of a blister beetle on the skin, or the discharge of the body fluids, is a vesicle within the epidermis. There is slight hyperemia in the underlying dermis. The powerful hemolytic toxalbumin of the small chrysomelid beetle is used on poisoned arrows by the South African bushmen.

Moths and Butterflies (Lepidoptera). One family of butterflies and several families of moths have caterpillars (larvae) that are equipped with poison hairs. These specialized setae enter into the epidermis between the cells and cause necrosis of the cells, exudation of fluid and fibrin to form an epidermal vesicle, and migration of lymphocytes, eosinophils, and polymorphonuclear leukocytes into the underlying dermis (Foot; Tyzzer).

Bees, Wasps, Hornets, and Ants (Hymenoptera). The fluid of the venomous glands of the hymenoptera is forced into the tissues through the sting and there sets up a local inflammation characterized by edema, hyperemia, and infiltration with lymphocytes and polymorphonuclear leukocytes.

In an occasional person bitten by a flea or a wasp, death results within thirty minutes, frequently within five minutes. At autopsy there are edema of the lungs and petechiae in the adrenal and in the serous membranes (Dyke).

Scorpions. Immediately or within a few hours after the bite of a scorpion the patient complains of headache, nausea, vomiting, and profuse perspiration. Death occurs in one to ten days in about 25 per cent of the patients. Findings at autopsy are limited to hemorrhage and edema of the lungs, brain, and other viscera (Basu).

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LVII

Diseases Caused by Miscellaneous Invertebrates and Vertebrates

In addition to the worms of the two phyla Platyhelminthes and Nemathelminthes and the arthropods, there are isolated species of many other phyla of invertebrates or vertebrates that directly or indirectly cause human disease.

Coelenterates. Two morphologic types of coelenterates are recognized: the polyp and the jellyfish. In the Mediterranean the sting of anemones produces a local area of inflammation, necrosis, and ulceration, known as "la maladie de plongeurs." Most jellyfish are harmless, but certain species, notably in the Mediterranean region and about the Philippine Islands, produce local and systemic lesions. In the rare fatal case there are hyperemia and edema of the viscera. The Portuguese man-of-war and the medusa of east Florida produce similar lesions.

Echinoderms. Echinoderms are injurious to man in three ways: (1) trauma from penetration of the spines, (2) the presence of toxic substances in the spines of some species, and (3) toxicity of ingested ovaries or eggs of some species (Earle).

Fish. Fish play a three-fold role in the causation of human disease. There may be: (1) intermediate hosts for helminths, notably the broad tapeworm and the liver fluke of Japan and China; (2) directly poisonous on ingestion of the flesh; and (3) venomous by bite, sting, or contact.

Poisonous Flesh. Most examples of poisoning following the ingestion of the flesh of fish belong in the field of food poisoning, since they result from secondary bacterial action. There are, however, a few fish whose flesh, in the fresh state, is poisonous (Gudger). In addition the flesh of other fish may become poisonous because of feeding on certain poisonous medusae and corals (Macht and Spencer).

Bite, Sting, and Contact. In some spiny fish such as the sting rays and the teleosts a slime is secreted (Evans) which causes a local inflammation of the skin, with at times systemic symptoms (Bayley). Fish of the genus *Muraena* have well developed poison glands and sacs in relation to teeth. The electric rays (Torpedinidae) produce paralysis by sending a powerful electric current through the victim. Some of the sting rays (Trygonidae) inject tetanus bacilli as well as venom into the depths of the wound.

Reptiles. Ophidism. In fatal cases of ophidism or snake-bite the anatomic changes are in general inconspicuous. At the site of the bite there are edema and hemorrhage. Petechiae or ecchymoses are present in many of the viscera, in the serous membranes, and in the brain. The brain is edematous. Microscopically swelling and hyalinization of the walls of the small blood vessels are seen, especially at the site of the bite and in the brain. There are perivascular hemorrhage, and desquamation and dissolution of the endothelial cells of the small blood vessels. In some capillaries there are hyaline thrombi (Rotter).

VENOM. Venoms are complex mixtures of toxic and antigenic principles of enzymes. The toxic principle is protein in nature, and antivenoms have been developed and successfully used in treatment. Toxic principles show remarkable affinities for specialized tissues (Noguchi). The signs and symptoms depend on the relative amount of the various toxic principles in the venom of the snake. The mortality varies from 10 to 35 per cent.

Lizards. The only venomous lizards are the Gila monsters, *Heloderma suspectum*, found in Arizona and New Mexico, and *Heloderma horridum*, in southwest New Mexico. Dyspnea, convulsions, and paralysis follow rapidly after

a bite from one of these apparently lethargic animals.

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PART III

DISEASES CAUSED BY PHYSICAL AGENTS

LVIII

Diseases Caused by Physical Trauma: Medicolegal Pathology

Mechanical trauma results from the action of force, and, according to the Galilean definition, force is that form of energy which changes or tends to change the state of rest or uniform motion of a body (Moritz).

Many factors control the extent and nature of the injury to the animal organism from mechanical trauma. The more important of these are the momentum of impact, expressed in terms of the size and speed of the impacting body and the time over which it is applied to the tissues, and the resilience of the tissues. The plasticity of the striking object is also a factor, in that a greater degree of injury is inflicted by a mass of ice than by a similar mass of water. The size of the area struck is of importance. An equal amount of energy onto an area 1 sq. cm. in size will produce a more severe lesion than the same total energy expended over 10 sq. cm. Finally there is the question of the transmission of the impact through the tissues. A person who falls on the palm of the hand may sustain a fracture of the neck of the humerus. The force of the impact is transmitted through the bones to the weakest point—at the shoulder. Blows over the hollow viscera may be transmitted to the structures within; a blow on the abdomen may so raise the intra-abdominal pressure that there is rupture of the intestine, the liver, or the spleen.

Wounds Produced by Mechanical Injury

Abrasions. An abrasion is a superficial interruption in the continuity of the epidermis and dermis—in lay terms it is a scratch. There are loss of epithelium and slight hemorrhage into the dermis. The defect is soon filled with a fibrinous exudate, which clots and forms the typical brown scab.

Contusions. In a contusion there is extravasated blood in the dermis and subcutaneous tissues without rupture of the continuity of the surface. It is usually produced by impact or by pressure. Hemorrhage is observed microscopically, separating the structures of the dermis. If the extravasated cells are collected in a local, tumorlike mass, it is known as a "hematoma." If they collect in the dermis or at the dermo-epidermal junction, it is colloquially known as a "blood blister." There is a progressive change in the color from red to dark red, blue, dark blue, brown, yellow, and yellowish green. The extravasated cells are phagocytized by monocytes and the contained hemoglobin converted to hemosiderin and hematoïdin. In general, hemosiderin appears within twelve to twenty-four hours, hematoïdin in from four to five days, and in minor contusions all of the extravasated cells should be engulfed within six to seven days.

Lacerated Wounds. A laceration is a tear of the tissue, usually caused by a crushing or stretching force. The most common lacerated wound is that which involves the skin where it is stretched over a superficial bone. The term "laceration" is also applied to tears in the internal viscera produced by an impact on the surface of the body. Thus a sudden, forceful flexion of the thorax on the abdomen may lacerate the liver or spleen.

Incised Wounds. An incised wound is one produced by pressure or friction of a sharp edge against the tissues. In contrast with contusions and lacerations, the incised wound is associated with little damage to the adjacent tissues, and if the edges are approximated, it will heal quickly.

Stab and Puncture Wounds. Rigid, slender objects may perforate the skin, subcutaneous tissue, and may even enter the viscera. Hat-

pins, knives, splinters of glass, and fragments of wood or metal are sometimes responsible for fatal puncture wounds, inflicted intentionally or accidentally. The danger of the wound is entirely dependent on the viscus perforated. If a major vessel or the heart is incised, death results within a few minutes from an exsanguinating hemorrhage. If the intestine is perforated, peritonitis may follow within a few days (Hamilton and Duncan).

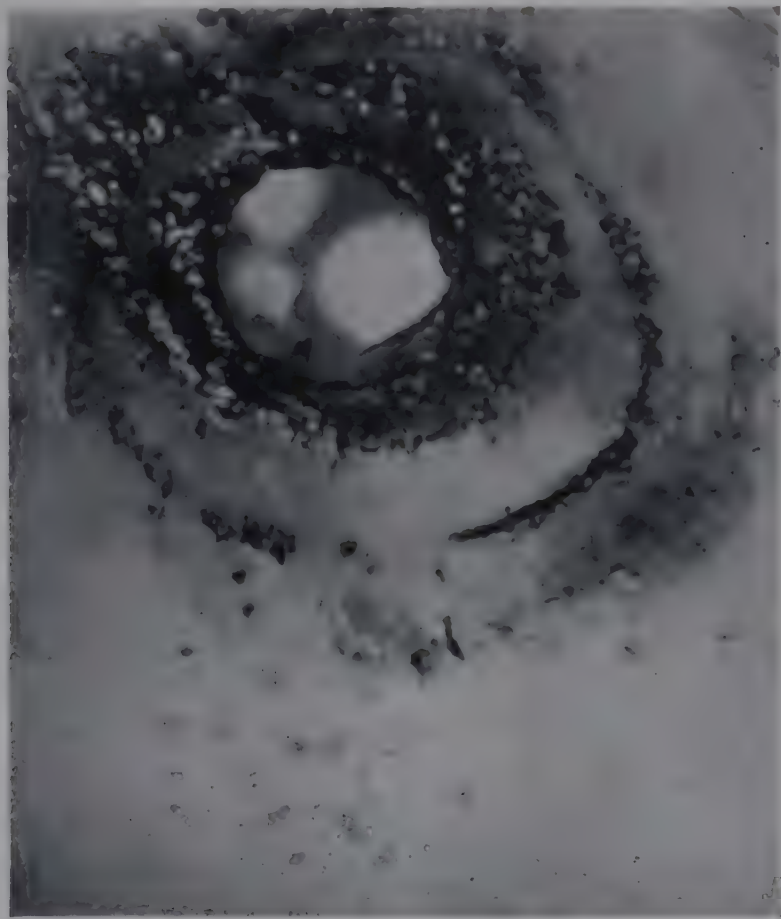


Fig. 250. Wound of entrance of bullet photographed on infra-red sensitized plate. (Photograph by courtesy of Dr. Alan R. Moritz.)

Injury to the Viscera by Blunt Impact. The absence of a wound or contusion on the surface of the body should not be taken as evidence that no internal injury occurred. A blow on the abdomen or thorax may injure the viscera without producing a visible contusion of the abdominal wall (Poer and Woliver; Sigler). A blow on the head may fracture the skull or produce a cerebral hemorrhage without appreciable hemorrhage or laceration of the scalp.

Wounds Produced by Bullets

The type of wound and the amount of destruction produced by a bullet depend on the type of ammunition, the velocity of the bullet, and the nearness of the muzzle.

Wound of Entrance. As the bullet strikes, the skin is stretched for a moment before perforation. The wound of entrance is therefore smaller in diameter than the actual bullet. On the clothing or on the skin about the wound of entrance there is the so-called "contact ring." Within this region, roughly twice the diameter of the hole, there are minute lacerations of the skin and subcutaneous tissues. Embedded within the skin are small fragments of the bullet and particles of the powder used. This contact ring can be well demonstrated in an infra-red photograph. If the muzzle of the gun is closely applied to the skin, the tissues beneath the wound of entrance are torn by the expanding gases.

Wound of Exit. The wound of exit is usually larger than the wound of entrance, and is irregular in shape. Three factors contribute to this characteristic picture. The bullet may meet resistance within the body and become flattened so that it is actually larger when it leaves through the skin. The bullet loses velocity and may start to wobble, thus tearing a larger hole. It may even come out sideways. Thirdly, pieces of hard tissue such as bone may be torn loose and be ejected through the wound of exit.

The Track of the Bullet and Internal Injury. The destructiveness of a moving bullet depends upon the amount of energy that it expends during the passage through the tissues. A large bullet will meet more resistance, use up a greater amount of energy, and thus produce more internal injury than a small one. If the bullet encounters dense tissue, such as bone, cartilage, and connective tissue, in contrast with fat, it again will use more energy and produce more damage. The more a bullet wobbles, the more energy is expended in traveling through the tissue, and hence more extensive damage results. A bullet traveling through the heart or any other hollow viscus filled with fluid exerts an explosive force and pushes the fluid away from the track. This explosive force may be sufficient to rupture a hollow viscus, even the heart and aorta.

Traumatic Injury of Bones and Joints

A fracture is the breaking of a bone or joint. If the line of fracture passes through the epiphyseal line, it is known as an "epiphyseal separation." If the bone is separated

into two parts it is designated as a "simple fracture," and when there are three or more parts it is designated as a "comminuted fracture." If the break extends only part way through the bone, it is called an "incomplete" or "greenstick fracture," or an "infracture." When a piece of the broken bone passes through the skin surface, the term "compound fracture" is applied.

A *dislocation* is the complete and persistent displacement of the articular surface of one of the bones of a joint from that of its fellow. A *subluxation* is an incomplete dislocation, in which the normal relation of the articular surfaces is disturbed, although they remain partly in contact. A *sprain* is a temporary subluxation in which the articular surfaces have returned to their normal positions, with some damage to the ligaments, tendons, and muscles about the joints. A *sprain fracture* is a sprain in which a small portion of one of the bones has been pulled off.

Causes of Fractures, Dislocations, and Sprains. The direct and immediate cause of all of these conditions is physical trauma, exerted directly on the bone, as by the fall of a heavy object and crushing of the tissues and bone, or transmitted to a bone from a distance, as in fracture of the humerus from a fall on the outstretched palm. Predisposing factors are important, and they are concerned with the strength of the bone. The strength of the bone depends in large part on the content of calcium, and any disease which brings about a withdrawal of calcium from the bones makes them more susceptible to injury—senile osteoporosis, hyperthyroidism, and hyperactivity of the parathyroid glands. The maintenance of normal structure and strength of a bone depends on constant use. When a person is bedridden for weeks or months, the bones undergo atrophy, and one of the bones may fracture a few days after he has recovered and is beginning to walk. The imperfect formation of bone seen in osteogenesis imperfecta may render the bones more susceptible to traumatism during birth. Localized destruction of bone, as by primary or metastatic tumors, bone cysts, and the lesions of osteitis fibrosa cystica, may form the basis for a fracture. A paralyzed or partially paralyzed extremity is more liable to be injured and possibly fractured, since it cannot be moved from the path of injury as quickly as a

normal extremity. When a fracture occurs through a previously diseased bone, it is customary to designate it as a "pathologic fracture."

Pathologic Anatomy and Repair of Fractures. Unfortunately the word "fracture" connotes only the idea of injury to bone, while in fact the injury to the surrounding soft tissue is often far more important than the break itself in determining the treatment and the ultimate prognosis. When the break occurs, a number of blood vessels, small and large, are interrupted, and blood is poured out into the space between the two fractured ends. This blood soon clots and forms the basic framework from which repair proceeds. If the two ends of the fractured bone are displaced, additional tissue is torn, with consequent hemorrhage and necrosis. The inept physician or the inexperienced lay person may bring about injury of the surrounding tissue from clumsy manipulation of the broken bone. Fibroblasts from the surrounding tissue and young capillary blood vessels grow into the clotted blood. Mononuclear cells invade the area and remove the dead tissue. Finally the two bony ends are held together by a loose connective tissue with a moderate amount of intercellular collagen. The fibroblasts may become round and take on the appearance of a chondroblast. The collagen swells and presents a picture similar to that of the ground substance of cartilage. This tissue does not represent true cartilage, and should therefore be designated "chondroid tissue." Chondroid and fibrous tissue constitute the primary callus.

The final step in the repair is the replacement of the primary callus by bone. This is accomplished by a combination of endochondral bone formation and membrane bone formation. Capillary vessels from the surrounding periosteum and endosteum invade the chondroid tissue and replace it with osteoid tissue. With resumption of activity and the assumption of stress by the bone, the trabeculae and cortex are rearranged to withstand the usual mechanical force to which the bone is subjected. If the two fragments have been accurately apposed, the repair may be so perfect that after some six to twelve months a microscopic section will not reveal any deviation from normal.

Nonunion. For any one of a variety of reasons a fracture may fail to heal. If the blood

clot between the two broken ends becomes liquefied because of secondary infection, the fibrin network for the subsequent growth of fibroblasts is not present, and the callus forms slowly or not at all. If a piece of living tissue, muscle, or fascia becomes interposed between the broken ends, the callus cannot grow across, and a *false joint* or *synarthrosis* develops. Extensive damage to the surrounding soft parts or comminution of the fractured ends results not only in a greater amount of necrotic tissue but also in impairment of the blood supply to the part, both of which may delay the union of a fracture. In fractures involving a joint, with rupture of the synovial membrane, large quantities of synovial fluid are poured into the space between the frac-

lesions, such as perforation of the bladder or rectum, puncture of the pleural cavity or lung, or laceration of the meninges or the brain. The middle meningeal artery courses within a canal formed of bone, and fracture of the skull in this region (the temple) tears this large artery and results in a serious extradural or subdural hematoma. In the vertebral column, fracture of a vertebral body, with displacement posteriorly or the ejection of a fragment into the spinal canal, may sever the cord and result in permanent paralysis below the level of the lesion.

Volkman's Ischemic Contracture. In a rare instance some weeks or months after the fracture of an arm, the extremity becomes practically useless and atrophic, and the muscles

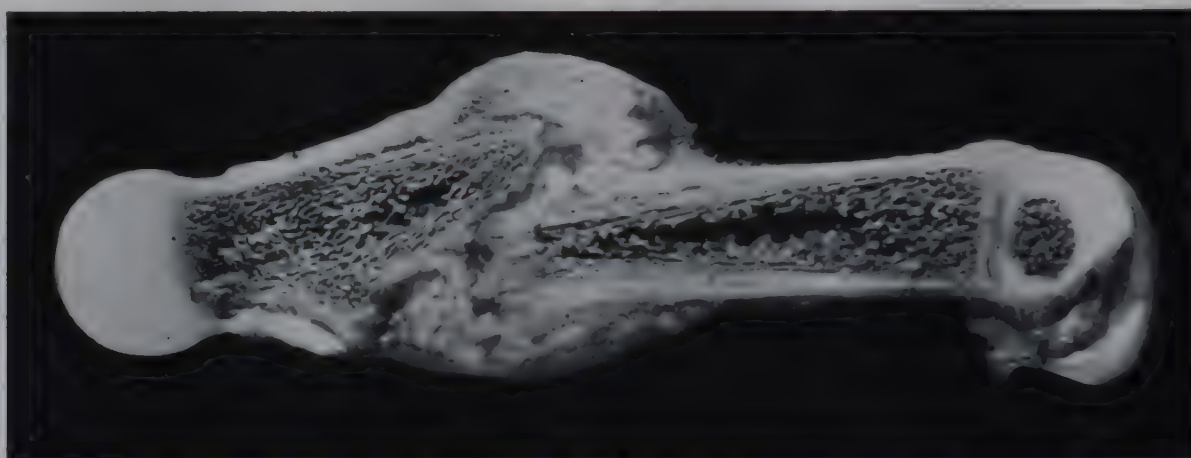


Fig. 251. Healing fracture.

tured bones, and may interfere with the formation of the clot and the proliferation of the surrounding fibrous tissue. In experimental animals and probably in man the proper healing of a bone depends on an adequate supply of calcium, phosphorus, and vitamin D. Similarly the development of the primary callus, composed of modified collagen, depends upon an adequate supply of vitamin C. In an occasional case of nonunion of a fracture, there is no demonstrable cause.

Complications of Fracture. *Infection.* As has been pointed out, an infection may interfere with healing through lysis of the clot about the broken bone. Of greater importance is bacterial invasion of the bone itself, and the establishment of osteomyelitis. This is far more common in compound than in simple fractures.

Injury to Muscles and Soft Tissues. In fractures of the abdominal, thoracic, and cranial walls, penetration of the sharp fragments of bone into these cavities may produce serious

are firm and cannot be moved. The body of the muscle is replaced by fibrous tissue, with only an occasional atrophic muscle fiber. It is believed that this results from interruption of venous return with a maintenance of the arterial supply, either from extreme edema about the fracture within an inelastic skin or from an overly tight plaster cast (Foisie).

Ossification of Muscle and of the Hematoma. Occasionally a hematoma formed about a fractured bone undergoes organization and calcification. Rarely the surrounding injured muscle undergoes ossification to produce the lesion known as "myositis ossificans" (p. 966). This latter condition is more frequently seen in simple damage to muscle without fracture of bone.

Injury to Blood Vessels and Nerves. In addition to the usual tearing of vessels incident to a fracture, comminuted fragments may penetrate and sever blood vessels and nerves, resulting in additional hemorrhage or gangrene of the extremity below the level of the

fracture, and paralysis. In fractures not accurately apposed, nerves and vessels may be caught in the fibrous callus, with production of the same clinical effects: paralysis and anesthesia.

Injury to Joints. Traumatic Arthritis. Fractures occasionally occur at the ends of the bones, so that one of the lines of fracture enters a joint cavity, with interruption of the continuity of the articular cartilage. If this occurs in a person with tabes dorsalis, Charcot's joint may develop. If it occurs in an otherwise normal person, it may heal in the usual way. In a small number of patients with

Dislocations. Repair of a dislocation is accomplished by reestablishment of the continuity of the joint capsule and proliferation of fibrous tissue in the stretched tendons. This repair may be inadequate, so that tendons and ligaments remain longer than normal and the joint cavity larger, and recurrent dislocation is to be expected. This is particularly common in dislocation of the humerus in young persons. Rarely, the joint surface of one bone from a dislocated joint may penetrate the skin and this is then called a "compound dislocation."

Parachute Injuries. Most injuries occur as the jumper makes contact with the ground and



Fig. 252. Diagrams illustrating the reinforcing arches of the skull. (LeCount and Apfelbach: J.A.M.A., Vol. 74.)

a fracture through a joint, the syndrome known as "traumatic arthritis" develops, in which there is pain on motion and relief of this pain at rest. The synovia is thickened, and there is an increased quantity of fluid within the joint cavity.

Acute Traumatic Atrophy of Bone. When a bone is placed in a cast or sling, a certain amount of atrophy and osteoporosis is expected to develop. Rarely, however, there is widespread and advanced osteoporosis involving not only the fractured bone, but all of the surrounding bones. It is most common in the bones of the hands and feet (Miller and deTakats).

Fat Embolism. The bone marrow of the long tubular bones of the extremities is normally composed of fat. Fracture or other mechanical trauma may force globules of fat into the veins and produce fat embolism of the capillaries of the lung, the brain, and the heart.

are fractures about the ankle (Tobin, Cohen, and Vandover).

Fracture of the Skull

Fracture of the skull deserves more consideration, even in a textbook of general pathology, than fractures of other bones, because of the peculiar mechanism of fracture, the extent of the fracture lines, the proximity of the brain, the frequency of cerebral injury, and the commonness of fatal complications. The skull is formed from several bones, and the suture lines along which they unite are relatively weak (Moritz; Levinson).

Mechanics of Fracture. The common mechanism of a fracture of the skull is a blow to the head by some object, with the head or the object or both in motion. Less commonly the head is crushed between two solid objects. At the moment and at the site of impact the wall of the skull is slightly flattened. The

skull of a child is resilient and recoils without fracture. In an adult, if the flattening is sufficient the bone fractures. The lines of force from the site of the impact are transmitted through the vault and base, and the fracture line will follow the path of least resistance. These paths are through the vault between the reinforcing pillars; through the base within the fossae, not at the junctions of the fossae; and along the suture lines. All lines directed toward the base will converge on the body of the splenoid bone (LeCount and Apfelbach).

Types of Fracture. The terms "fracture of the vault," "fracture of the base," and "combined fracture of the skull" are self-explanatory. If a piece of bone is displaced inward and presses on the brain, the preferred designation is "depressed fracture." The terms "comminuted fracture" and "compound fracture" are used in the same sense as in other parts of the body. If the fracture line is single, the adjective "linear" is employed, while if the crack branches extensively, the adjective "composite" is applied.

Cerebral Contusion and Contrecoup. At the moment of impact the skull is pressed against the brain, and this may cause contusion of the meninges and brain, especially if the head is held firmly and cannot recoil. If the head is free, a fraction of a second after the impact, the momentum of the blow throws the brain forcibly against the skull opposite the point of impact. Contusion here is known as a "contrecoup injury." A blow on the back of the head thus results in contrecoup lesions of the tips of the frontal and temporal lobes where the brain is forced against the irregular bone of the anterior and middle cranial fossae (Courville).

Clinicopathologic Correlation. The most important clinical consideration in fracture of the skull is the injury to the meninges and brain (McGregor). The response to any injury is edema or hemorrhage or both. This means an increase in the size of the brain within a bony cavity of limited size, and hence the appearance of the signs and symptoms of increased intracranial pressure. By x-ray examination and the elicitation of localizing signs, it is frequently possible to delineate the fracture lines and the areas of trauma or hemorrhage. Hemorrhage into the subarachnoid space can be demonstrated by the presence of blood in spinal fluid withdrawn through

a lumbar puncture. If the fracture line passes through an accessory nasal sinus, air may gain entrance to the cranial cavity—*pneumocephalus* (Rand).

Causes of Death. The most common cause of death is laceration of the brain and subdural hematoma. There follow in order of frequency: cerebral concussion, extradural hemorrhage, meningitis, and secondary bronchopneumonia (Vance).

Sequelae. If there is extensive damage to the brain or hemorrhage into the meninges, permanent loss of some part of cerebral function is to be expected (Munro). Certain instances of epilepsy have resulted from cerebral injury, and some success in treatment has attended the surgical removal of the hyperirritable focus.

"Punch Drunk." Following injury to the head, especially in prize fighters, there is frequently a characteristic train of clinical symptoms: slight paralysis of one or both legs, unsteadiness of gait, uncertainty in equilibrium, and slight mental confusion. In the brain there are multiple small hemorrhages in the perivascular spaces (Martland).

Miliary Infarcts following Cerebral Injury. In some persons following injury to the head, small microscopic foci of hemorrhagic or anemic infarction appear after twenty-four to forty-eight hours. They are found in all parts of the brain, but especially in Ammon's horn. It is generally believed that reflex vasoconstriction is the cause (Helfand).

Fracture of the Vertebral Column. Fractures of the vertebrae are produced by hyperflexion, hyperextension, and vertical compression. The most common sites are the second cervical, fifth and sixth cervical, and first lumbar vertebrae. In about one-half of cases there is injury to the spinal cord and permanent paralysis below the point of fracture. In healing, callus may impinge on the cord or on the major nerves as they pass through the foramina (Jefferson and others). Study of sections above and below the traumatized segment shows degeneration of the cerebripetal and cerebri-fugal tracts respectively.

Extradural Hemorrhage

Extradural hemorrhage is most frequently seen as a complication of fracture of the skull, and especially in fractures through the greater

wing of the sphenoid bone, in the region where the anterior branch of the middle meningeal artery courses in a 1 to 3 cm. long groove or tunnel through the bone. Clotted blood accumulates in the extradural space and lifts the dura from the bone. The blood clot is a space-consuming lesion, and there are the signs and symptoms of intracranial pressure and deepening coma. In the classical case there are an initial short period of unconsciousness from the shock of the injury, a second period of consciousness, followed some

is a clot of blood in the subdural space loosely attached to the dura and to the arachnoid. There is a pressure deformity of the cerebral hemisphere in direct proportion to the size of the hematoma. In from one to two weeks there is beginning proliferation of fibrous tissue in the dura mater, and in a period of four to six weeks this fibrous tissue grows over the surface of the hematoma and completely isolates it from the arachnoid. There is thus formed a sac bounded by a thin layer, 0.5 to 1 mm. thick, of fibrous tissue, known as the

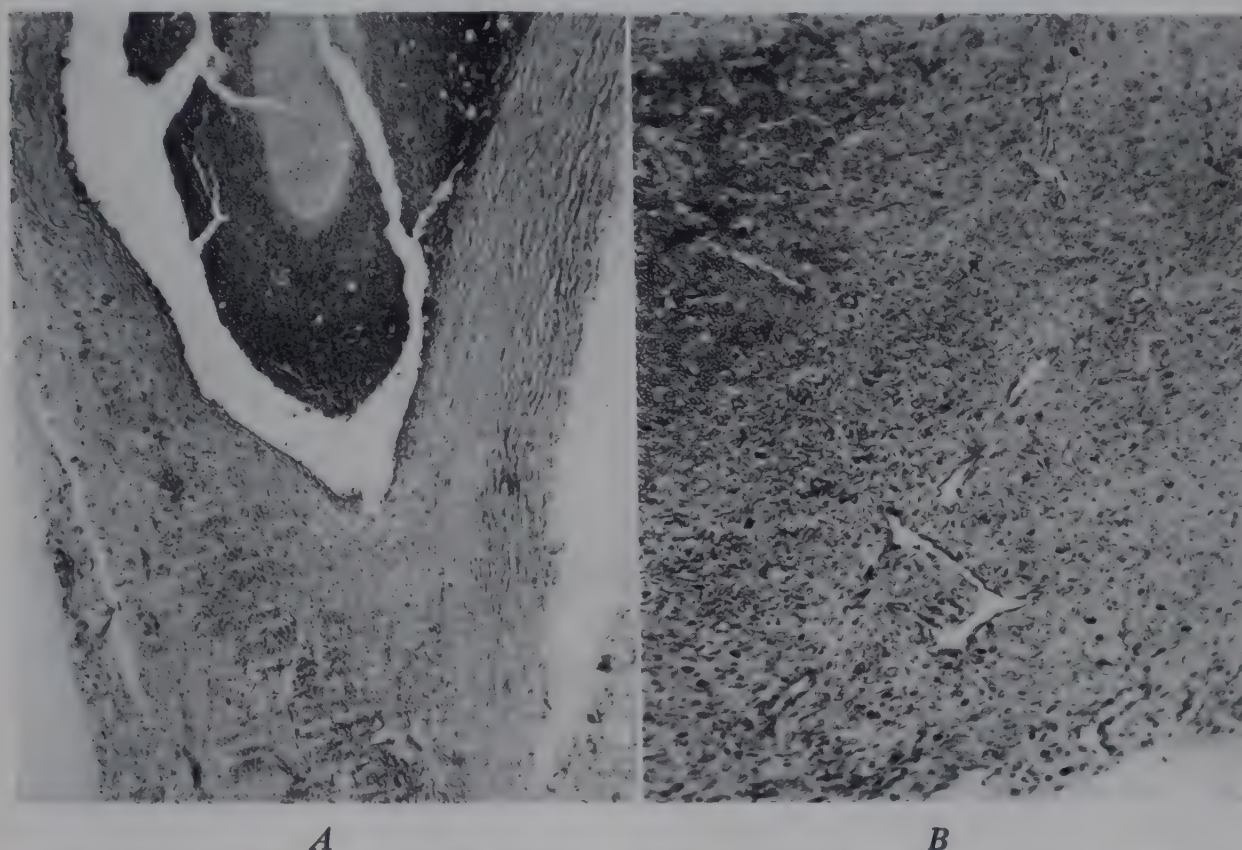


Fig. 253. Subdural hematoma. *A*, Dura and neomembrane enclosing the hematoma. *B*, Granulation tissue and giant capillaries in neomembrane.

hours or days later by a third period of deepening coma, as the clot increases in size. Focal signs are usually present, and because the lesion is almost always unilateral, there is a demonstrable shift in the position of the ventricles on ventriculography. The pupil on the affected side is dilated (Gurdjian and Webster).

Subdural Hematoma

The condition known now as "subdural hematoma" was originally described by Virchow under the title, "pachymeningitis hemorrhagica interna chronica." In view of the fact that there is no evidence of inflammation, the former term is preferable.

Pathologic Anatomy. For several days following the development of the lesion there

"neomembrane" (Fig. 253). The center of the sac is filled with dark brown fluid or clotted blood. Microscopically, the neomembrane is seen to be composed of dense collagenous tissue with many large, thin-walled, sinusoidal blood spaces. Within the neomembrane small hemorrhages from rupture of these giant capillaries are seen (Leary).

Incidence. Causal Factors. The increased incidence in alcoholics and in some paretics and epileptics suggests that injury to the head is a causal factor: the alcoholic falls and stumbles into things, the epileptic and paretic fall on the floor, and the older man is slower to avoid injury than the young man. In the early cases it can be demonstrated that the source of hemorrhage is a small bridging vein passing across the subdural space from the arachnoid to the dura mater (Fig. 254). In an

occasional instance a vein within the arachnoid may rupture into the subdural space. It is only rarely that the veins and arteries in the dura mater are ruptured except in association with fracture of the skull. A history of actual fracture of the skull can be secured in only a small percentage of instances.

Clinicopathologic Correlation. Following injury to the head with rupture of a blood vessel, there is a temporary period of unconsciousness or confusion, followed by a period

transient state, instantaneous in onset, with widespread symptoms of a purely paralytic kind and no evidence of structural cerebral injury, which is usually followed by amnesia for the actual moment of the accident.

Pathologic findings at autopsy are extremely limited. There is no fracture of the bones of the skull and no conspicuous extradural, subdural, or subarachnoidal hemorrhage. The ganglion cells and glial cells show no pathologic change.

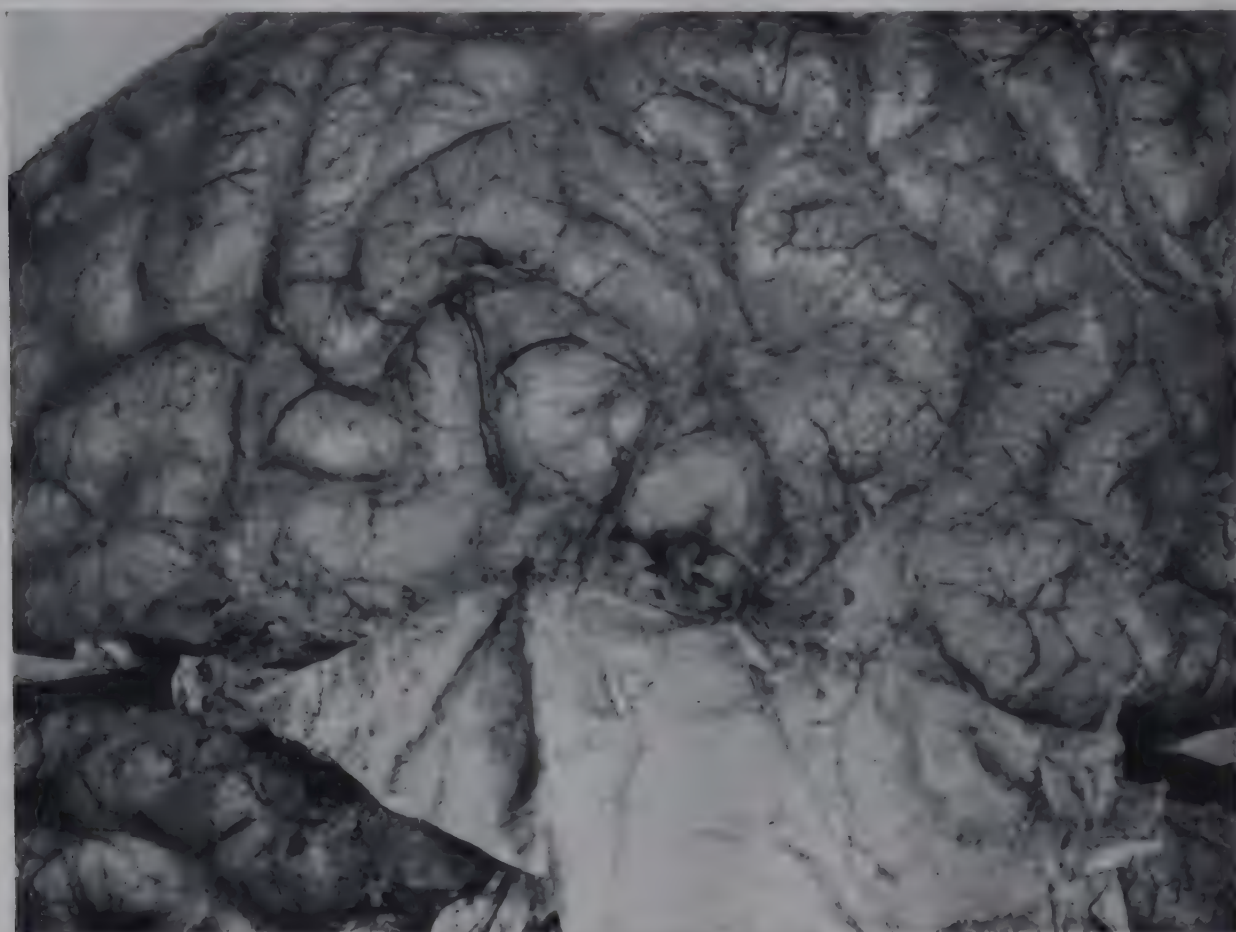


Fig. 254. Bridging vein, rupture of which is the usual cause of subdural hematoma. (Armed Forces Institute of Pathology, Neg. No. 74051.)

of from four to six hours in which there are few symptoms. The patient then becomes unconscious from the increase of intracranial pressure. In some instances there is no period of unconsciousness, and the patient comes to the physician some months later with a complaint of headaches, and blurring of vision, resulting from the increase of intracranial pressure (Munro). The steady growth in the severity of these symptoms indicates that the hematoma continues to enlarge after it has once been surrounded by the neomembrane (Zollinger and Gross).

Cerebral Concussion

Following injury to the head a symptom complex known as "concussion" sometimes develops. This term designates an essentially

Pathogenesis. Numerous unsuccessful attempts have been made to reproduce the disease in animals. The concept of acceleration concussion has been proposed by Denny-Brown and Russell. They found that when the unfixed head of a monkey or cat is struck by a heavy mass with a velocity of approximately 8 feet per second the typical clinical picture of concussion results. There are no pathologic changes in the brains of these animals except for petechiae in a few. Thus, concussion is to be looked upon as a syndrome produced by the sudden attainment of a relatively high velocity of the head itself.

The Crush Syndrome

During World War II, bombing of civilian areas led to the recognition of a new disease

process known as the "crush syndrome." In a typical case the patient is buried for several hours under the debris of a fallen building, with one or more limbs severely compressed. On admission to the hospital the patient's condition may be good, but within a few hours, the general picture of shock sets in. There is edema of the crushed limb. Within one to two days there are the signs and symptoms of renal insufficiency, and death usually occurs from uremia.

Pathologic Anatomy. At autopsy the significant pathologic findings are in the kidneys and in the crushed limb. The kidneys are large and weigh from 200 to 250 gm. The capsule is tense, the renal parenchyma is dark red, and on section a quantity of fluid blood pours from the surface. The cortex is increased in thickness. The markings are retained. The glomeruli are normal. The epithelium of the proximal convoluted tubules and to a limited extent of the descending limb of Henle's loop shows cloudy swelling and necrosis. In many foci there is beginning regeneration of the tubular epithelium, as well as mitoses. Within the lumens of the tubules there are typically eosinophilic, brown, granular or homogeneous masses, similar to those seen in the kidneys following a hemolytic transfusion reaction (Gillespie, Nivem, and Dunn). In the crushed limb there is edema, with hemorrhage into the interstitial tissue. The muscles are friable and soft. Necrosis of individual muscle fibers is observed microscopically (Bywaters and Beall; Patey and Robertson).

Chemical Changes. There are definite and consistent changes in the chemical constituents of the blood and the hemoconcentration usually associated with shock. With renal insufficiency there is an increase of the non-protein nitrogen and a decrease in the carbon dioxide combining power. There is also a remarkable decrease in the serum sodium with a corresponding increase in the serum potassium.

Causal Factors. The basic factors in the renal injury are two: hemoglobinuria or myoglobinuria from the injured muscle, and vasoconstrictive renal ischemia. The latter causes oliguria which leads to aciduria, which in turn results in precipitation of pigment casts. Therapy logically then consists of prevention of renal ischemia by treatment of the shock, pressure bandaging of the injury to

prevent absorption, and promotion of flow of an alkaline urine (Corcoran and Page).

Clinicopathologic Correlation. The uremia is probably due to injury to the renal epithelium and blockage of the tubules by the hemoglobin casts. The primary role of compression in inducing the syndrome is supported by the observation that if the injured limb is immediately placed under pressure of 40 to 60 mm. of water the syndrome does not appear (Duncan and Blalock; Patey and Robertson).

Traumatic Asphyxia

Following violent thoracic compression, such as crushing between vehicles, there occasionally develops a deep cyanosis anteriorly of the upper part of the thorax, of the neck, and of the head; and posteriorly of a triangular area between the scapulae, of the shoulders, and of the neck. At autopsy numerous small and large hemorrhages throughout the muscle and tissues of the neck are seen (Bonnin).

Arteriovenous Aneurysm

Pathologic Anatomy. An arteriovenous aneurysm is an abnormal communication between an artery and a vein. The proximal artery is dilated, and the wall is atrophic. The proximal vein is dilated, and the wall is hypertrophic. There are hypertrophy and dilatation of the heart, most conspicuous on the right side, and in patients who have died directly as the result of an arteriovenous aneurysm there is advanced chronic passive hyperemia in all of the viscera. Careful dissection of the arteries about the aneurysm shows an abundant collateral circulation.

Causal Factors. The most common cause of an arteriovenous aneurysm is a penetrating wound, from either a firearm or a sharp instrument. Where an artery, a vein, and a bone are in intimate contiguity, fracture of the bone may lead to the establishment of an arteriovenous aneurysm. On occasion a saccular aneurysm may bulge toward and rupture into an adjacent vein.

Physiologic Considerations and Clinicopathologic Correlation. The clinical findings may be roughly divided into those caused by the presence of an aneurysmal sac, those caused by the rush of blood through a small

opening between an artery and a vein, and those caused by a large arteriovenous shunt. In an attempt to compensate for the shunt there are an increase in blood volume, an increase of the minute volume output of the heart, a marked increase in the minute volume flow in the vena cava, an increase of venous pressure in the involved region, and a fall in diastolic blood pressure. On compression of the arteriovenous communication, the systolic pressure immediately returns to normal and there is a bradycardia known as the "Branham phenomenon," probably caused by the increase in the diastolic pressure. After months or years anoxia leads to ulceration of the skin, fibrosis of the subcutaneous tissues, pigmentation of the skin, and intermittent dilatation. It is highly significant that the heart which has undergone dilatation and hypertrophy in response to an arteriovenous aneurysm returns to normal size on surgical relief of the condition (Reid and McGuire; Holman). Arteriovenous aneurysms are most common between the femoral artery and the femoral vein, but have been reported in all parts of the body. Subacute bacterial endarteritis about the aneurysm has been observed (Touroff, Lande, and Kroop).

Pulsating Exophthalmos. An uncommon type of arteriovenous aneurysm is that between the carotid artery and the cavernous sinus following fracture through the base of the skull. The transmission of the arterial pulse to the cavernous sinus and in turn to the ophthalmic vein produces protrusion of the eye and pulsation of the entire eyeball (Marten and Mabon).

Traumatic Fat Necrosis

Injury to the subcutaneous adipose tissue as by mechanical trauma, by hypodermic injection or hypodermoclysis, or by surgical incision may lead to necrosis of fat and a characteristic picture known as "traumatic fat necrosis." The lesions are more common in the female breast, probably because of the greater amount of fat and the liability of this structure to injury. There is a poorly outlined, stony hard mass, adherent to the skin. In early stages there are necrosis of fat cells, hemorrhage, and infiltration with lymphocytes and leukocytes. Later, fibrosis is prominent, and within the fibrous tissue there are giant cells

and lymphocytes. Clinically, the differential diagnosis from carcinoma may be difficult. The absence of pain, the history of trauma, and the corpulence of the patient are important distinguishing features (Lee and Adair).

Drowning

Drowning is a special type of asphyxia in which external respiration is blocked by spasm of the larynx or by filling of the lungs with water. In the former there are few anatomic changes, while in the latter the respiratory passages are filled with a frothy fluid. After submersion for days the tissues become macerated and autolysis sets in.

Chemical Changes. If water enters the lung before the heart stops, the salt content of the blood will be altered. With sea water the amount of sodium chloride in blood from the left ventricle will be greater than in blood from the right ventricle. With fresh water the reverse is true (Gettler). Determination of magnesium may also give valuable information.

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LIX

Diseases Caused by Changes in Atmospheric Pressure

The physiologic processes of both plants and animals are adapted to life at a barometric pressure that does not deviate greatly from 760 mm. of mercury. Compensation for the changes within the range found in the populated parts of the earth is easily made, but adjustment to great increases or decreases, and to sudden changes, is frequently inadequate.

Mountain Sickness

Physiologic Considerations. At high altitudes there are an increase in the number of red blood cells and in the amount of hemoglobin per unit of blood and per red cell, an increase in the size of the red cells, an increase in the viscosity of the blood, an increase in the resistance of the red cells to hemolysis, an increase of the serum proteins, a slight increase of the hydrogen ion concentration of the blood, an increase in the total ventilation through the lungs, a hypertonus of the vegetative nervous system, a decrease in the arterial oxygen saturation, a decrease in the carbon dioxide alveolar pressure, and a decrease in the alkaline reserve of the blood.

Pathologic Anatomy. There are few actual anatomic alterations in the person adapted to high altitudes. Sections of the bone marrow reveal more active erythropoiesis, but beyond this there is nothing definite.

Clinicopathologic Correlation. The oxygen deficiency expresses itself as the clinical syndrome of mountain sickness, and most of the symptoms result from anoxemia of the brain. These are painful periodic headache, a sensation of fulness of the head, hot flushes on the face, photophobia, injection of the ocular mucosa, blurring of the vision, scotoma, lacrimation, vertigo, dizziness, general sweating, and vomiting. The pulse becomes slower, and

there is intense cyanosis. The spinal fluid pressure is greatly increased, and the condition may progress rapidly to coma and death. On the other hand the anoxemia of the brain may be expressed in a transient hemiplegia, monoplegia, or aphasia. All of these signs and symptoms are reversible (Hurtado).

Caisson Disease

When the animal organism is subjected to an increase in atmospheric pressure, greater quantities of all of the gases in the air are forced into solution in the blood. When the pressure is suddenly released, the blood can no longer dissolve the excessive gas, especially nitrogen, and it is liberated into the tissues and within the blood vessels.

Pathologic Anatomy. If death occurs within a few hours, the only findings are bubbles of gas within the blood vessels, and in the soft tissues, especially about the joints and in fat. If the patient lives for some days, weeks, or months, pathologic changes in the nature of ischemic necrosis are found. The most important of these are in the central system, especially in the spinal cord, where small and large foci of myelomalacia are present. Less commonly there are small or large foci of necrosis of bone (Kahlstrom, Burton, and Phemister).

Clinical Aspects. Gas within the branches of the superior mesenteric artery, with interruption of the blood supply to the intestine, results in severe pain, which bends the victim over; gas in the internal ear, the labyrinth, cochlea, and semicircular canals produces the general symptoms of Menière's syndrome; gas in the branches of the pulmonary artery produces edema of the lung; and gas in the small capillaries of the skin and in the sweat glands causes itching, mottling, and blotching of the skin. The emboli of nitrogen in the ves-

sels of the central nervous system and within the substance of the brain and cord may occur at any point, and therefore produce any single or combined group of localizing signs. The permanent damage to the cord is reflected in paralysis or weakness of the lower extremities and paralysis of the bladder and rectum (Thorne).

Decompression Illness

A condition similar to caisson disease is decompression illness, which occurs in aviators. At sea level from 1000 to 1400 cc. of nitro-

cc. in the second hour while the patient breathes 100 per cent oxygen (Fig. 255).

Oxygen Poisoning

A concentration of oxygen above 60 per cent in the respired air, especially if under pressure or with a high humidity, is toxic to animals and man.

The initial sign is facial pallor, followed by nausea, vertigo, malaise, apprehension, and terminating in mental depression or excitability and convulsions identical with those of idiopathic epilepsy (Donald).

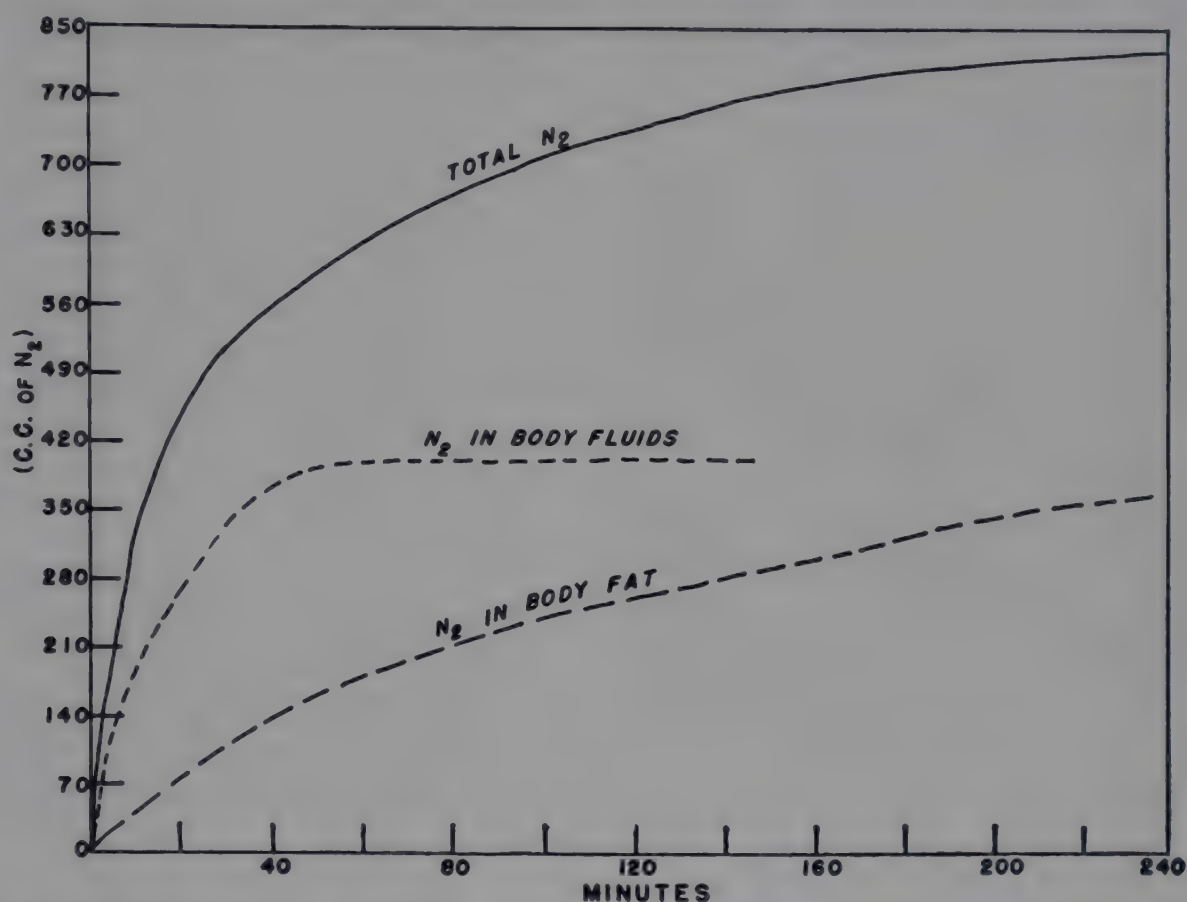


Fig. 255. Velocity of elimination of nitrogen during breathing of oxygen. (By courtesy of Howard R. Bierman: Washington University Medical Alumni Quarterly, Vol. VI.)

gen is physically dissolved in the body fluids. In an ascent to 30,000 feet, about 900 cc. of this nitrogen must be blown off through the lungs because of the decrease in the partial pressure of nitrogen in the atmosphere. If the ascent is rapid, the lungs are not able to dispose of the nitrogen, and it appears in the tissues as air bubbles. The location of the bubbles and the resultant clinical signs and symptoms are the same as those in caisson disease. The most satisfactory method which has yet been developed to prevent decompression illness is the inhalation of pure oxygen. It has been estimated that approximately 550 cc. of nitrogen can be removed from the body in the first hour, and an additional 200

The outstanding anatomic change is pulmonary edema, which may be followed by bronchopneumonia. There are slight changes in the electro-encephalographic tracing, and definite depression of the metabolism of surviving tissue slices in the following order of sensitivity: brain, spinal cord, liver, testis, kidney, lung, and muscle.

The Air-Blast Syndrome

Pathologic Anatomy. Following explosions, particularly the explosion of bombs and aerial torpedoes during World War II, persons were found dead without a mark of violence of any sort on the outside of the body. At autopsy

numerous small and large petechiae and ecchymoses are seen throughout the lung. Hemorrhage into the alveoli is observed microscopically. In addition, petechiae may be found in the brain and in other organs. Occasionally there is rupture of the spleen or of the liver.

Causal Factors and Pathogenesis. When a bomb explodes, there is a wave of compression and of suction which travels radially from the point of explosion. The intensity of both the compression and the suction decreases as it moves farther away. At first it was thought that the damage to the lung was brought about by the compression and suction transmitted through the respiratory tree; but experimental study has shown that the major damage is produced by compression of the chest. The petechiae in the lung are frequently directly beneath the ribs, and there is only slight evidence of tearing of the lung such as would be produced by a change in pressure within the respiratory tree. The application of a thick layer of rubber over the thorax prevents the development of the lesion in animals (Fulton).

Clinical Aspects. Many people survive the effects of a blast and show few symptoms. The physical signs are those of a patchy consolidation of the lung based on the foci of hemorrhage. The air of the blast contains carbon monoxide, and this aspect must be considered in the treatment (Zuckerman).

The Water-Blast Syndrome

Pathologic Anatomy. The human body has roughly the same density as water, and pressure waves in water are transmitted through the tissues and not reflected. If the pressure wave encounters a cavity filled with air, however, the force is changed into kinetic energy in the tissue lining the cavity, and a disruptive effect results. Thus in persons immersed in the sea in close proximity to an underwater explosion, there are extensive anatomic changes in the lungs and intestines—tearing of the tissues and hemorrhage—but fewer lesions in the solid viscera and brain and little or no damage to the soft tissues and bones (Auster and Willard).

Clinical Aspects. The injury to the intestine is reflected in a clinical syndrome coming on ten to forty-five minutes after the explo-

sion, of intermittent or continuous abdominal pain, vomiting, and diarrhea. Hemorrhage into the lung is clinically manifested by hemoptysis. The neurologic signs may be similar to those of concussion. Similar lesions have been produced in animals (Clark and Ward).

Motion Sickness

Motion sickness is a clinical syndrome characterized by anorexia, excessive salivation and sweating, vertigo, nausea, vomiting, and headache, which may appear while a person is riding in a car, elevator, boat, or other vehicle. The cause is obscure, but a basic hypersensitivity of the vegetative nervous system seems probable. Vestibular, auricular, olfactory, or proprioceptive stimuli may serve as the precipitating cause. Objective physiologic and anatomic changes are not conspicuous. Increased irritability of the pylorus and absence of peristalsis in the intestine have been observed by fluoroscopic examination and mild gastritis by gastroscopic study (Schwab).

Audiogenic Trauma

Intense sound waves may injure structures in the middle or internal ear and cause temporary or permanent deafness.

In certain strains of mice auditory stimulation results in seizures of frenzied running and convulsions, rarely terminating in death (Halt).

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LX

Diseases Caused by Radiant Energy

Radiant energy is that form of energy which is propagated through space. Like any other form of energy it may be expressed in energy units such as the erg, joule, or calory. There are many types of radiant energy, from the short cosmic rays to the long electric waves.

Man has utilized many of these forms of radiant energy, for both medicinal and industrial purposes. He has further invented and built machines for the artificial production of x-rays, of radioactive emanation, and of visible light. The solar spectrum extends from 2900 Å to 50,000 Å. As the result of the loss in space and absorption in the atmosphere of the earth, only 1 per cent of the ultraviolet radiation, 40 per cent of the visible radiation, and 59 per cent of the infrared radiation strikes the surface of the earth.

Excessive Environmental Heat

When man is exposed to excessive environmental heat, the mechanism for the dissipation of heat may be inadequate or may become injured, and any one of three clinical syndromes may result: heat stroke, heat exhaustion, or heat cramps.

Heat Stroke. Death from heat stroke is more common in the very young and the very old. The pathologic changes are: early onset of postmortem rigor and decomposition, fluidity of the blood, extreme hyperemia of the viscera (especially the lungs), and dilatation of the right ventricle. There are petechiae in many tissues. Cloudy swelling of the liver and kidneys is the rule. Hemorrhage into the myocardium especially about the bundle of His is believed by some to be the immediate cause of death (Wilson). If death is delayed, a diffuse bronchopneumonia is usually found. Similar changes have been observed in patients

treated with artificial hyperthermia, and in association with certain conditions that produce extreme hyperpyrexia (MacNeal).

Heat Exhaustion. In this condition there is a subnormal or normal temperature, and the signs and symptoms result from exhaustion and failure of the heart. Pathologic findings are those of acute cardiac failure—passive hyperemia of the viscera.

Heat Cramps. The pathologic changes of heat cramps are not known, but the fact that they can be relieved or prevented by the ingestion of adequate amounts of sodium chloride indicates that they result from a physiologic alteration in the sodium and chloride ions (Talbot).

Burns

A burn is an injury inflicted on the body by a degree of heat higher than is compatible with normal metabolism in the part affected. The lesions are generally classified into four types, designated as first- to fourth-degree burns, characterized by erythema, formation of vesicles, formation of an eschar, and charring of the tissues respectively (Pack; Erb, Morgan, and Farmer; Aldrich).

Pathologic Anatomy. Pathologic changes of a *first-degree burn* are essentially those of inflammation—dilatation of vessels, exudation of fluid, and margination and exudation of leukocytes. In the repair of this minimal lesion, there may be desquamation and hyperpigmentation, which disappears in a few weeks.

In the *second-degree burn* there are all of the changes of a first-degree burn plus irreversible coagulation necrosis of the superficial epidermis. This leads to the exudation of fluid into the epidermis and the formation

of a vesicle. The fluid approximates the composition of blood plasma. In healing, epidermization occurs under the vesicle, and the integrity of the surface is restored.

In a *third-degree burn* the entire epidermis and a part of the dermis, except for the rete pegs, are destroyed. An inflammatory reaction takes place in the exposed dermis, and the surface is covered by a fibrinous exudate. The epithelium regenerates from the rete pegs, but there may be some slight scarring because of destruction of the superficial dermis and loss of some of the epidermal appendages.

The *fourth-degree burn* is characterized by destruction of tissue down to or into the subcutaneous fat and muscles. The burn appears as a brown eschar (dry heat) or a white, coriaceous area (moist heat, as by live steam). The immediately surrounding tissues show varying grades of first-, second-, and third-degree burns. After a few days the necrotic tissue drops out and exposes the deeper tissues, which are the seat of an intense, acute inflammation. Repair is accomplished by proliferation of granulation tissue to fill the defect, and growth of epithelium from the edges. The epidermal appendages do not regenerate, and a scar, free of hair, sweat glands, and sebaceous glands, covered by an atrophic layer of epidermis, is the result.

Systemic Lesions. At autopsy in fatal cases hyperemia of many viscera, notably the brain and lung, is observed. If the patient lives for some days, bronchopneumonia is the rule. The adrenals are greatly enlarged, and are red and soft. The cortical cells are necrotic. In the liver there are cloudy swelling, fatty degeneration (Buis and Hartman), and central necrosis has been frequently seen, directly caused by the tannic acid formerly used in the treatment of burns (Wells, Humphrey, and Coll). The physiologic and chemical changes are those of shock. A negative nitrogen balance is conspicuous (Taylor, Levenson, Davidson, Adams, and MacDonald). Acute ulcers of the stomach and duodenum are seen (p. 656).

Clinicopathologic Correlation. In third-degree burns, with exposure of the free nerve endings in the dermis, there is extreme pain, while in fourth-degree burns with an eschar, there is little local pain. The necrotic tissue of a burn is often the seat of secondary bacterial infection. The lesions in the kidneys cause a moderate degree of renal insufficiency.

The most important clinical consideration is the restoration of the intravascular plasma.

Death in a Conflagration. Frequently the pathologist is asked to determine if death occurred before or during a fire. Death during a fire is recognized by the presence of carbon monoxide in the blood, particles of soot in the respiratory tract, and true blisters of the skin (Dutra).

Effects in the Lungs. When the temperature of air about the body is sufficient to produce almost instantaneous burning of the skin and upper respiratory mucosa, there may be sufficient residual heat in the inspired air to cause injury to the lower respiratory tract. The important effects are edema of the glottis and hemorrhagic edema of the central regions of the lung (Moritz, Henriques, and McLean).

Excessive Environmental Cold

The pathologic effects of an excessive exposure to cold may be classified in two categories: irreversible death of the tissues (frost gangrene), and reversible changes (chilblains) (Lewis).

Frost Gangrene. The onset of frostbite or frost gangrene is characterized by pallor of the skin, believed to be caused by contraction of the blood vessels. It occurs most commonly in the exposed and terminal parts of the body, such as the fingers, toes, ears, and tip of the nose. Later the skin turns purple or black, and in twenty-four to forty-eight hours epidermal vesicles appear, and the involved part is swollen. The tissues are extremely edematous, soft, and purple, and there are thrombi in the vessels and early changes of necrosis. Crystallization of the water within the cells and changes in the salt content of the cytoplasm may be contributory causes of necrosis. If the part is not removed surgically, a sharp line of demarcation appears, and the necrotic tissue mummifies. A characteristic feature is the lack of any repair (Friedman and Kritzler).

The important determining factors are low temperature, high velocity of the wind, and lack of protection by clothing. Persons with advanced vascular disease are more susceptible (Brahdy). The fluid that passes out into the tissue is essentially blood plasma, and the loss may be sufficient to precipitate the syndrome of shock similar to that seen following burns (Harkins and Harmon).

Chilblains. Exposure to less severe cold or to cold with a high humidity causes a partially reversible condition. The part is dark blue, and when brought to a warm place remains blue, swells, and becomes painful. After some days the epidermis peels off in areas, and the tissues return to normal in a few weeks.

Cryoglobulinemia. Rarely in a patient with leukemia, myeloma, and other diseases, there is an abnormal globulin in the serum which precipitates on cooling. This globulin agglutinates the red cells in vitro and it is possible that this phenomenon is responsible for the excessive sensitivity to cold of the patients (Schwartz and Jager).

Paroxysmal Cold Hemoglobinurias. This symptom complex occurs in two distinct forms: syphilitic paroxysmal cold hemoglobinuria and paroxysmal cold hemoglobinuria. The former is caused by a cold-warm hemolysin unique to patients with syphilis, recognized by the Donath-Landsteiner test, while the latter is related to excessive amounts of cold hemagglutinins in the serum. Pathologic studies are inadequate (Becker).

Immersion Foot

Immersion foot or trench foot, a condition of major importance in both World Wars, results primarily from exposure to cold and moisture, and is aggravated by constrictive shoes, prolonged dependency, immobilization, and deficient nutrition.

Pathologic Anatomy. There is an initial vascular change of peripheral vasoconstriction and relative hypothermia. Immediately after the part is exposed to warmth, there is an intense hyperemia with excessive vasodilation and transudation of fluid, white cells, and red cells to the tissues. Both gross and microscopic studies reveal the alterations of ischemia—degeneration of nerves and other sensitive tissues and frequently thrombi in vessels showing vacuolation or necrosis of the walls (Friedman).

Physiologic Considerations. After an initial injury, the reaction and repair persist for a long time, so that the patients are unable to adapt normally to environmental cooling (Burch, Myers, Porter, and Schaffer). Subsequent submaximal exposures may precipitate gangrene.

Porphyria

The porphyrins are basic constituents of the respiratory pigments—hemoglobin, cytochrome, catalase, and others. There are four possible isomers of each porphyrin, of which two, designated as I and III, occur in nature.

Porphyria is an “inborn error of metabolism” in which abnormal porphyrins appear in the body fluids. Two main types are recognized—the light sensitive and the acute intermittent (Watson).

Light Sensitive Porphyria. This is a rare condition in which exposure to light results in erythema and vesicle formation in the skin. Repeated exposures lead to extensive fibrosis and mutilation of the face and hands.

Acute Intermittent Porphyria. The urine in this condition contains porphobilin and its precursor porphobilinogen. The patients are not light sensitive but complain of varied abdominal and nervous symptoms. There are degenerative changes in nerve cells of the anterior horn of the spinal cord and sympathetic ganglia.

Secondary Porphyria. In many conditions there is an increase of urinary coproporphyrin—type I in infectious hepatitis and the cirrhosis resultant therefrom, and type III in primary cirrhosis, in refractory anemias, and in poliomyelitis.

Ultraviolet Rays

In man, except under experimental conditions, it is difficult to separate the effects of ultraviolet rays from those of visible rays and infra-red rays.

Injury to the Skin. After exposure to intense solar radiation, as on a beach or in the mountains, there is an immediate erythema which spreads over the entire body and is not confined to the area exposed. This is caused by the infra-red rays, and is a simple effect of heat on the skin. About twelve hours after the exposure there is a second reaction, characterized by redness and swelling of only the exposed area. This is the effect of the ultraviolet rays. Hyperemia and edema of the dermis are seen microscopically. The epidermal cells are swollen, and small vesicles may form. In more severe reactions there is hemorrhage into the dermis. After some days the keratinized layer of the skin desquamates, and there is increased pigmentation.

Injury to the Eye. Photo-ophthalmia. The eye is even more sensitive to ultraviolet rays than is the skin. Within a few hours after excessive exposure of the eye, the cornea becomes cloudy as the result of the migration of polymorphonuclear leukocytes into the transparent part of the cornea. The epithelium on the surface undergoes necrosis and desquamation or lysis. There is a similar change in the epithelium on the anterior surface of the lens. In the process of repair, blood vessels may grow into the cornea.

Snow Blindness. The ultraviolet rays focused by the lens strike the macula, and if they are of great intensity there may be tran-

gosterol in the tissues and blood of the skin into vitamin D₂ (calciferol). A secondary change is the elevation of the serum calcium, which accounts for the satisfactory treatment of tetany with ultraviolet rays. In general, animals and children receiving an optimal amount of ultraviolet rays grow more rapidly, and wounds exposed to ultraviolet rays heal more quickly.

Roentgen Rays and the Rays of Radium

As therapeutic agents the short electromagnetic rays of x-ray and radium, the alpha

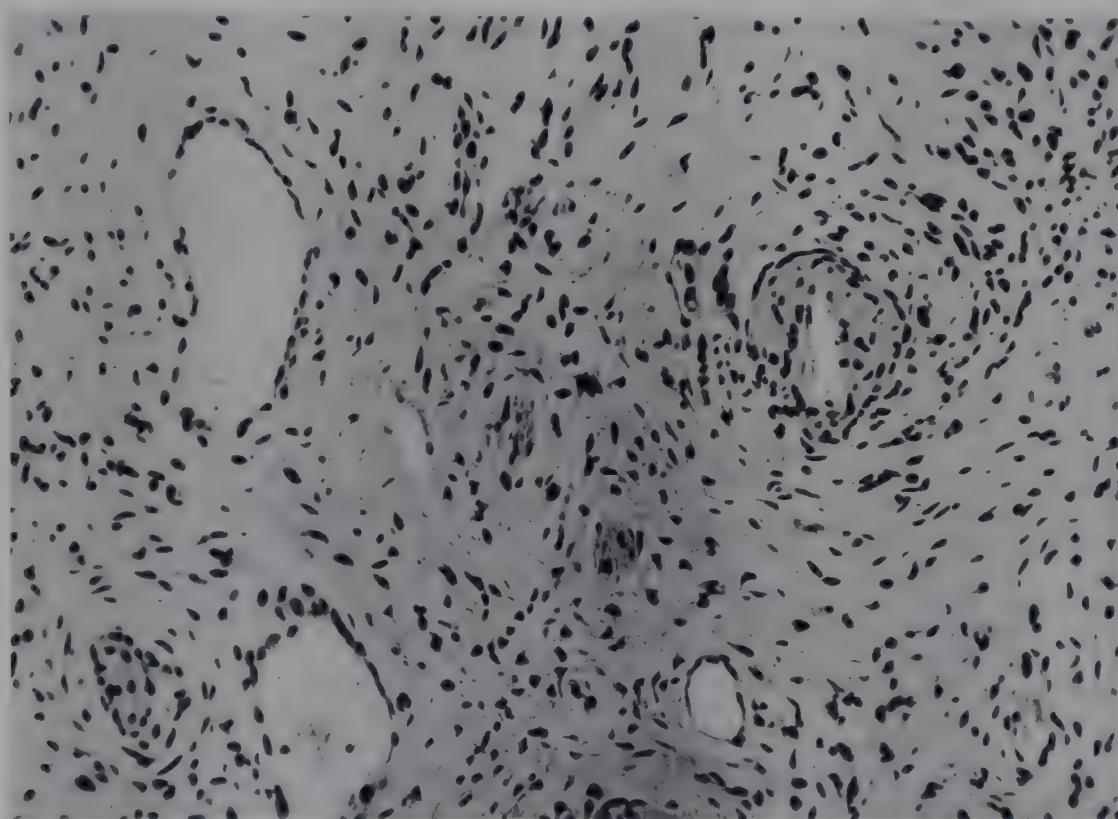


Fig. 256. Radiation reaction in cervix. Note the fibrosis, thickened arterioles and telangiectasis.

sient or permanent damage to the retina. This damage probably results from the heat generated by the absorption of the rays in the pigment layer of the retina.

Systemic Effects. There is no question that, at least psychologically, the human being feels better when exposed to light, and after having acquired a good tan of the skin. Scientific investigations of this problem have given inconsistent and irregular results. There are, however, two definite effects of ultraviolet light: an effect on calcium and phosphorus metabolism, and an effect on growth and the healing of wounds. The observation that children exposed to sunlight do not develop rickets is as old as the human race. The radiant energy probably prevents rickets by converting er-

particles (helium nuclei), and the beta rays (electrons) of radium and of artificially produced radioactive isotopes, and neutrons generated in the cyclotron have been used. Alpha particles are said to be 100 times as effective biologically as the beta rays, and a neutron beam of equal ionizing activity has a greater biologic effect than roentgen rays.

Within the therapeutic range, variations in wavelength do not produce qualitative differences in response. The character of the response is determined by the amount of radiation absorbed, the intensity of the radiation, and the tissue exposed (Warren).

Basic Reaction. The early anatomic response to irradiation is largely in the nucleus, although granularity and vacuolation of the

cytoplasm have been described. The nucleus is more sensitive while in mitosis than in the resting state. Further mitosis is inhibited, and the nucleus becomes hyperchromatic and pyknotic. After a time there are recognizable fragmentation of nuclei, abnormal or multiple nuclei, and multiple or unequal mitoses. Some of the injured cells die and undergo autolysis. Other injured ends, notably the fibroblasts, proliferate, and in some weeks or months the histologic appearance designated as "radiation reaction" is evident—fibrosis with hyalin-

twenty days, and as it fades is replaced by some degree of pigmentation. The cause is a change in the vascularity and in the interstitial tissue of the corium. Acute roentgen dermatitis comes on as the initial erythema begins to fade, and is a serofibrinous and hemorrhagic inflammation with desquamation of epithelium and occasionally ulceration. Doses of 400 to 500 r at 200 kilovolts produce temporary epilation in about three weeks, and permanent loss of hair is produced by larger doses. In the hair follicles there are



Fig. 257. Epidermoid carcinoma in a scar of a burn from roentgen rays. The irradiation was carried out in 1904, and the tumor appeared in 1939. (From the files of the Barnard Free Skin and Cancer Hospital.)

ization and giant bizarre fibroblasts, thickening and hyalinization of the arteries and arterioles, telangiectasis, abnormal endothelial cells, and atrophy of parenchymal elements.

Effects on Normal Tissue. It is rarely possible to deliver to a lesion adequate radiation without exposure of some normal tissue, hence the radiotherapist must be familiar with the many side-effects, some of which are undesirable.

Skin. The visible effect on the skin is an erythema produced by from 300 to 700 r, and divisible into two phases. An initial erythema develops in a few hours to three days, and is the result of direct injury of cells. A secondary erythema appears in ten to

vacuolation, cessation of mitosis, and necrosis of cells. The sweat and sebaceous glands are sensitive; and a month after a single dose that produces erythema, fewer glands and a heavy hyaline membrane about the remaining coils are evident by microscopic study.

Chronic roentgen dermatitis may be a hypertrophic or atrophic type. In the hypertrophic form there are hyperkeratosis, acanthosis, and absence or sparseness of hair follicles. The nails are brittle and deformed. In the atrophic form the skin is shiny, thin, and scaly, with many spider telangiectases. Epidermoid carcinoma may originate in any part of the hypertrophic form or in the edge of the atrophic form.

Hematopoietic Tissues. The bone marrow and lymph nodes are among the tissues most sensitive to irradiation. After a latent period of three to six days there is a depression of maturation of all cellular types (see Fig. 258). With small doses there is rapid recovery, first by the lymphocytes and last by the erythrocytes. Larger doses delay recovery, or may lead to irreparable damage and death from granulocytopenia, anemia, or purpura. Repeated damage and regeneration, as in those who work with roentgen rays, occasionally result in leukemia.

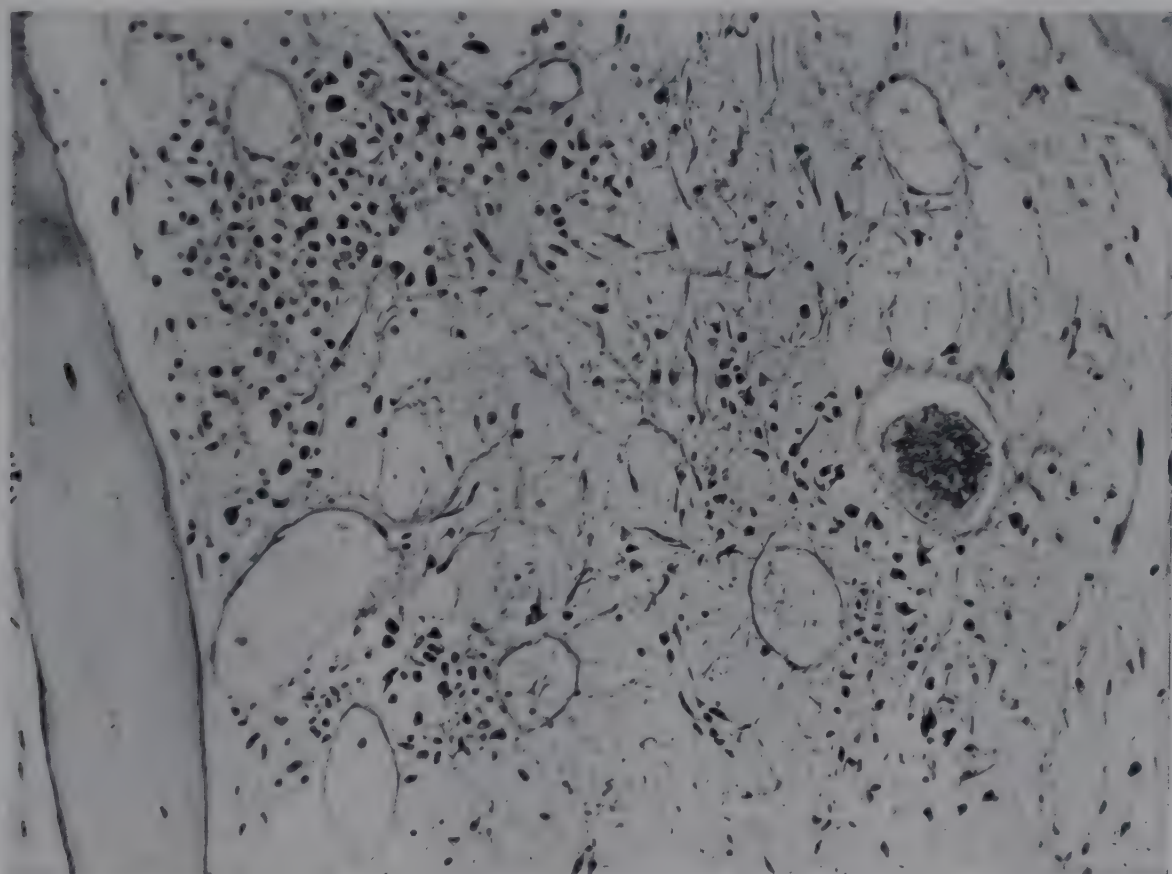


Fig. 258. Atrophy of bone marrow following irradiation.

Gastro-intestinal Tract. After exposure of the intestine there are conspicuous changes in the mucosa—degeneration of epithelial cells, hyperemia and edema, infiltration with lymphocytes and leukocytes, ulceration, vacuolation of muscle cells, and destruction of the lymphoid follicles. In the late stages there is the typical radiation reaction, occasionally with chronic ulceration. The salivary glands and pancreas are relatively radioresistant. In the liver there is primary degeneration, followed by fibrosis.

Respiratory Tract. The initial reaction in the lungs and bronchi is the same as in the skin. With larger doses a progressive fibrosis develops. The cellularity of the alveolar walls is increased. There are proliferation of anaplastic, cuboidal cells lining the alveoli, the

formation of a hyaline membrane, and increase of elastic fibrillae.

Urinary Tract. After large doses extensive tubular degeneration occurs in the kidney, followed by extensive interstitial fibrosis and hyalinization of the glomeruli. In advanced lesions there is renal insufficiency. The ureters and bladder are relatively resistant, but late ulcers of the bladder may result from irradiation.

Gonads. Both the ovary and testis are radio-sensitive. In the ovary edema and hemorrhage occur, with degeneration of the pri-

mordial and developing ova, and fibrosis. In the testis the germinal epithelium degenerates, and atrophic tubules filled with Sertoli cells remain. The interstitial cells are apparently relatively resistant. In both sexes sterility, either temporary or permanent, may result.

Nervous System. The peripheral nerves and the ganglion cells are highly resistant, but with large doses a vascular reaction may induce secondary changes of ischemia.

Heart. Fatty degeneration, edema, and cellular infiltration of the heart have been observed after irradiation delivered through the thoracic wall. At least in experimental animals there are also functional alterations—inverted T wave and auricular fibrillation or flutter.

Effect on Tumors. With present tech-

niques all tumors may be classified on a scale between radiosensitive and radioresistant. The factors which determine the response are manifold, and are not entirely understood. Certain neoplastic cells such as those of the lymphosarcoma are apparently inherently sensitive. Some cellular types in one organ are sensitive and in other organs are resistant. In general, resistance is associated with a high degree of differentiation, and sensitivity with embryonic structure and increasing anaplasia. Tumors in younger persons are apt to be more sensitive, while a tumor in a patient with anemia and emaciation is likely to be resistant. Tumors in relatively avascular tissues such as bone, cartilage, and fat, bulky tumors with foci of infarction and liquefaction, and infected tumors respond poorly (Stewart).

Since there is great individual variation, the ultimate determination of the sensitivity of a given tumor must be based on a study of the patient, or on biopsies before and after a test dose (Warren, Meigs, Severance, and Jaffe).

Irradiation Sickness. In some patients three to ten days after exposure to irradiation, especially over the abdomen, a symptom complex develops, characterized by weakness, nausea, vomiting, oliguria, bloody diarrhea, rapid feeble pulse, low blood pressure, and profound prostration. The cause of this delayed reaction is not known with certainty, but it would appear to be the result of the absorption of dead tissue, especially the products of autolysis of the intestinal mucosa. The pathologic changes are essentially those of shock (Moon, Kornblum, and Morgan).

The Effect of Roentgen Rays on Infection. Radiotherapists have for many years used roentgen rays with reported success in the treatment of both acute and chronic infections. The reasons for this beneficial action are obscure, especially since in carefully controlled experiments in animals roentgen treatment increases the size of the lesion, produces more necrosis, and enhances the invasiveness of the micro-organisms (Angevine and Tugle).

Neutrons

Neutrons are particles of matter of the same weight as the nuclei of hydrogen atoms and occur in the nuclei of all atoms except hydrogen. They ordinarily do not exist free

in nature, but may be obtained by bombarding atomic nuclei with high energy photons or atomic particles, as in a cyclotron.

The effects of neutrons on tissue do not differ qualitatively from those of roentgen rays. However, the quantitative effect is much greater. For example, the relative ratio of neutrons to roentgen rays for a threshold skin effect is in dosage units about 1 n to 2.5 r, while for late skin effects it is in the region of 1 n to 4 r, and for chronic effects it approaches 1 n to 15 r. In histologic terms these comparisons mean that the late epidermolysis, atrophy, and fibrosis are much greater after an early reaction which appears of safe degree. Injury to bone may proceed to necrosis and the late effect in the intestine may be fibrosis sufficient to prevent peristalsis.

Although some patients with cancer have been rendered free of the disease by treatment with neutrons, the side effects are so serious and incapacitating as to make doubtful the use of this form of therapy (Stone).

Explosion of an Atomic Bomb

Four major types of injury are observed in persons exposed to the explosion of an atomic bomb: air-blast, mechanical, heat, and radiation (Liebow, Warren, and De Coursey).

The effect of the air-blast is less than after ordinary high explosives. Rupture of the eardrum was observed in only 1 per cent of survivors at Hiroshima and Nagasaki. The mechanical injuries are the result of the widespread destruction of buildings and differ in no respect from similar injuries under other conditions.

The radiant heat produced in an atomic explosion is in extreme quantity, lasts for an exceedingly brief interval, and travels in a rectilinear path. Hence the burns are of the flash type. In repair, deep pigmentation remains for many months.

The changes produced by radiation are qualitatively the same as those resulting from roentgen rays. Early, up to one to two months, there are epilation beginning on the fourteenth to twentieth day, edema, congestion, hemorrhage, and bizarre epithelial cells in the intestine, atrophy of the testis, atrophy of lymphoid tissue, and depression of myeloid and erythroid activity in the bone marrow. The important clinical effects of these lesions are nausea,

vomiting, and diarrhea from the intestinal lesion, and increased susceptibility to infections and hemorrhage because of suppression of hematopoiesis.

Late there are more advanced stages of the same lesions with some regeneration as in the bone marrow. The usual causes of death are an ulcerative colitis and a necrotizing pneumonia. The lens of the eye shows swelling of cortical fibers and vacuolation, that is,

rent and the resistance of the tissues of the body also influence the pathologic change. A current which passes through the left side of the body or a current which passes through the brain is more dangerous than a current which is limited to the extremities or which passes through the right side of the body. Soft tissues offer less resistance to the current than bone; thus an electric current which enters one arm and leaves through the trunk or the extremi-

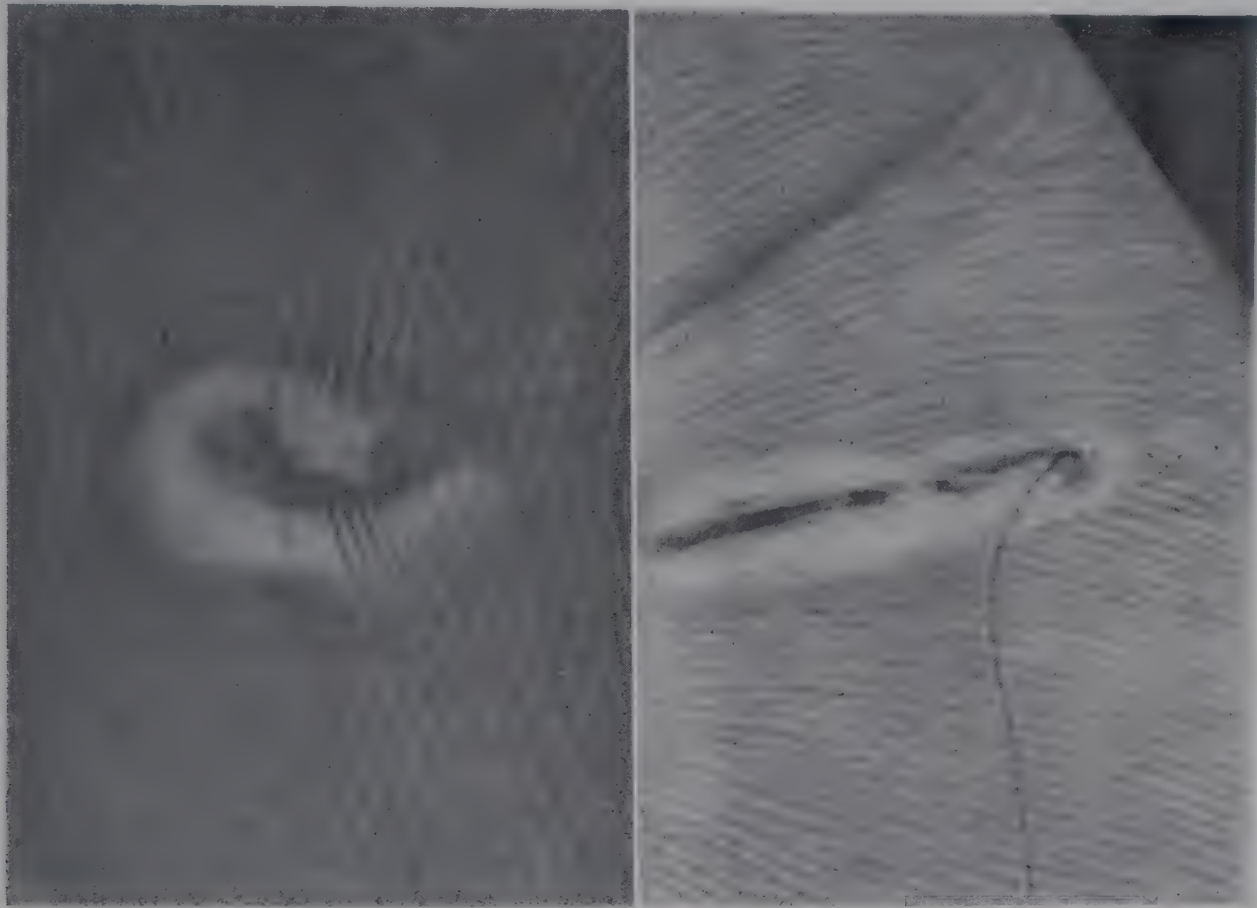


Fig. 259. On the left the point of entry and on the right the point of exit of an electric current. (Photographs by courtesy of Dr. Herbert Breyfogle.)

early cataract formation, after only twenty-four days.

Electricity

The pathologic and clinical effects of the introduction of an electric current into the animal organism are determined by a number of factors. The electric current may vary in voltage, amperage, or type. Currents of high tension introduce not only the factor of electricity, but also that of heat. Within the range of electric currents to which human beings are exposed, the alternating current is more dangerous than the direct. Currents of high frequency above 200 cycles per second and faradic currents rarely if ever produce fatal electrocution or injury.

The point of entrance and exit of the cur-

ties will produce greater damage at the elbow, where there is less soft tissue, than at any other point except the points of entrance and exit.

Pathologic Anatomy. The pathologic anatomy is conveniently considered under three sections: the mark of an electric current, the changes of death, and the alterations in persons who live for some hours or days or recover.

The *mark of entry* of an electric current is a round or oblong, rosettelike or linear, gray, white, or yellow elevation (Fig. 259). In the center there is a small craterlike depression, and the markings of the epithelium are completely obliterated. The hair is undisturbed. This mark is not always present, and it may be produced after death. *In persons who die* instantaneously or within a few minutes, the

principal pathologic changes are hyperemia and edema of the lungs, and numerous petechiae throughout the serous membranes. The lesions in persons in whom death is delayed or who recover may be divided into two categories: death of tissue caused by the direct action of the electric current, and secondary changes in tissue resulting from the passage of the current. The superficial burn is not essentially different from the burn produced by fire or heat, except that complications are rare. The late effects of the passage of an electric current are definite but inconstant. In the muscle the normal delicate striations are lost and replaced by broad, transverse, homogeneous bands. In peripheral nerves the myelin degenerates, and at times the axis cylinders are lost. In the brain chromatolysis takes place in the ganglion cells, the nuclei are displaced, and even actual necrosis occurs (Heilbrunn and Weill). Petechiae may be present. Of great importance are changes in the blood vessels. There is necrosis of a part or all of the wall, especially near the point of entry, with mural or occluding thrombi (Jaffe).

Physiologic Considerations and Clinico-pathologic Correlation. The pathologic effects of an electric current are produced in three general ways: by heat, by electrolysis, and by mechanical trauma. Heat of great intensity brings about charring of the tissues, while heat of moderate intensity results in the formation of steam within an area, and disruption of the tissues. It is probable that death of cells and loss of function of certain structures such as nerves may be caused by electrolysis. Physical trauma includes the tearing of muscles and even fracture of bones from the tremendous spasm induced by currents of high intensity. The cause of immediate death is not known with certainty, but central respiratory paralysis and ventricular fibrillation are the most important factors. The delayed healing of wounds and burns produced by electricity is probably the result of an inadequate supply of blood because of the thrombi in small and large blood vessels (Hesser).

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PART IV

DISEASES CAUSED BY CHEMICAL AGENTS

LXI

Diseases Related to Hypersensitivity: Hay Fever, Asthma, Serum Sickness

It has been known for over a century that contact with certain substances can alter the animal organism in a manner that will cause its tissues to react with increased intensity to subsequent contact with the same substance. This phenomenon is known as hypersensitivity.

There are two clearly defined types of hypersensitivity; the tuberculin type and the anaphylactic type. In the tuberculin type, typified by the tuberculin reaction in tuberculosis, passive transfer is not possible, and the reaction can be demonstrated in vitro. The anaphylactic type is characterized by passive transfer and with present techniques can be shown only in vivo (Rich).

The tuberculin type is manifested in many of the infectious diseases and is discussed in connection with each if pertinent. The anaphylactic type may in itself be the primary pathogenic agent in producing disease and is discussed in this and the succeeding chapter.

Hay Fever

Pathologic Anatomy. The chief pathologic change in hay fever is an acute inflammation of the nose. The mucous membrane is edematous and hyperemic. A thin mucus fills the cavities and runs profusely from the nares. Within the mucus are a few epithelial cells and eosinophils. In the tissues there are edema, dilatation of vessels, and infiltration with eosinophils, mononuclear cells, and a few polymorphonuclear leukocytes.

Causal Agents. A large number of pollens have been described as the cause of hay fever. In the United States the more common of the trees are American elm, cottonwood, and oak. Of the grasses, timothy, blue grass, and Ber-

muda grass are the commonest; and of the weeds, ragweed, sagebrush, Russian thistle, and English plantain.

Clinicopathologic Correlation. It is estimated that 2 to 3 per cent of all persons in the United States have hay fever. The swelling of the mucous membrane with consequent obstruction of the nose, and the hypersecretion of mucus because of the inflammation, are the outstanding clinical symptoms.

Atopic Rhinitis. Patients in whom it is not possible to demonstrate any sensitivity to pollens show clinical and pathologic changes in the mucous membrane of the nose identical with those of hay fever. In these persons nasal polyps (actually redundant edematous mucosa) are common, and both the secretion and the tissues contain many eosinophils. In about 50 per cent, sensitivity to some substance such as room dust or feathers can be demonstrated (Walsh and Lindsay).

Asthma

In cases which have been diagnosed as asthma during life, certain definite pathologic changes are found in practically everyone. On the other hand one or more of these same changes may be found in persons who did not have clinical asthma.

Pathologic Anatomy. The lungs are emphysematous, and in the larger bronchi the mucosa is swollen and pink or red, and the lumens contain large amounts of mucus. The walls of the medium-sized and smaller bronchi are thickened and the lumens decreased in diameter. The small lumens contain thick tenacious mucus, which may completely obstruct the passage. The lymph nodes about the trachea and bronchi are large and soft. There

is characteristic thickening and hyalinization of the basement membrane of the epithelium of the medium-sized bronchi. The epithelium itself is thickened and frequently shows ulceration or metaplasia. There is definite hypertrophy of the musculature of these bronchi, and the interstitial tissue between the muscle fibers is the seat of subacute or chronic inflammation. There are moderate fibrosis of the submucosa and infiltration with abundant

bronchial spasm, which, with secondary bacterial inflammation, in turn leads to the pathologic changes. The streptococcus is the most commonly found bacterium (Kämmerer and Weisshaar).

Clinicopathologic Correlation. The obstruction of the smaller bronchi and the emphysema are the basis for the profound dyspnea. It is not clear why the dyspnea should be paroxysmal.

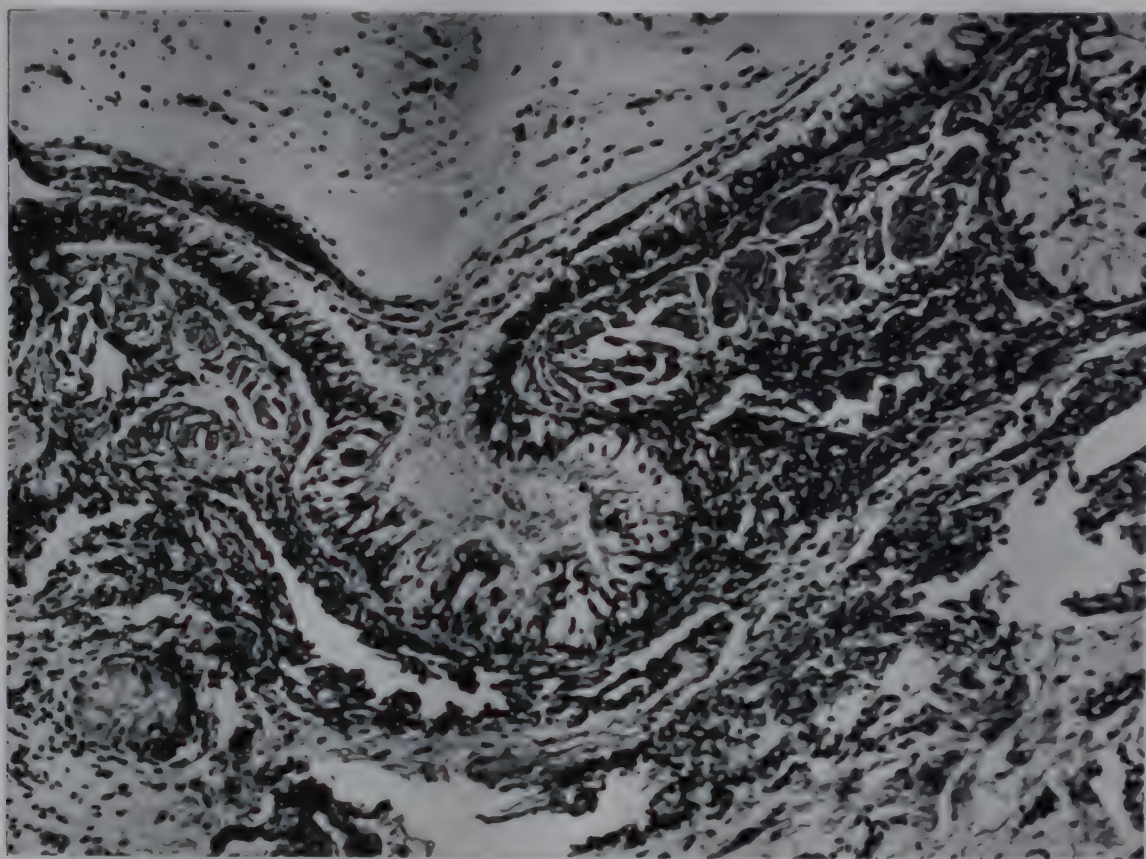


Fig. 260. Bronchus in asthma. Note excessive mucus, thickened basement membrane, and cellular infiltration.

eosinophilic leukocytes. Some of the glands of the bronchi are atrophic, while others are distended with mucus, and there is a widening of the orifices of the glands on the surface of the bronchi. In localized regions the bronchi are dilated to form saccular bronchiectasis (Thieme and Sheldon).

Incidence. Bronchial asthma occurs with about equal frequency in the two sexes and may be found at any age, although it is commonest in young adult life.

Causal Factors. It is customary to discuss the causes of asthma under two headings, bacterial and nonbacterial. In both types sensitivity is the mechanism, in the one case to the proteins of certain bacteria, and in the other case to any one of a wide variety of both organic and inorganic substances. Beyond this, it is difficult to define sharply the causes or the pathogenesis of asthma. It is possible that sensitization to these substances results in

Serum Sickness

Serum sickness is the reaction of the body to injection of a foreign protein, usually the serum of another species. It may take one of three forms: normal reaction, accelerated reaction, or immediate reaction.

Normal Reaction. The normal reaction is what is usually known as "serum sickness." Six to eleven days after the administration of a foreign protein there is an abrupt onset of malaise, muscular pains, nausea, vomiting, arthralgia, skin eruption, fever, edema, and enlargement of the lymph nodes. In more severe cases there are cardiac arrhythmia and signs of meningeal and cerebral irritation. Because of the low mortality there are only a limited number of pathologic studies. Rich observed an acute panarteritis in most organs similar to the lesion of polyarteritis nodosa. An acute interstitial myocarditis is probably

the basis for the cardiac changes and edema or hemorrhage in the brain for the cerebral disturbances. The rash is usually urticarial. The effusion into the joints contains polymorphonuclear leukocytes.

Accelerated Reaction. In the accelerated reaction the incubation period is one to three days, the onset is explosive, the symptoms are more violent, and the course is shorter. Circulatory collapse and respiratory difficulty are outstanding. It occurs in those who have an acquired sensitivity to the homologous protein.

Immediate Reaction. The immediate reaction is analogous to anaphylaxis in experimental animals. Sudden dyspnea, cyanosis, asphyxia, edema, circulatory collapse, convulsions, and profuse urticaria are the common signs and symptoms. Pathologic changes are not characteristic. The blood is dark red and unclotted. The heart is dilated. The lungs are voluminous, and the alveoli are generally or focally distended. The mucous membrane of the respiratory tract is edematous. The veins of the splanchnic region are dilated. In the terminal bronchioles and alveoli there is a moderate to advanced edema. The only reliable method of objective proof of anaphylactic death is the use of serum for a Prausnitz-Küstner reaction (Lund and Hunt).

Incidence. Why serum sickness develops in some persons and not in others is not entirely explained. Immediate and accelerated reactions occur in persons who are sensitized, and are more frequent in asthmatics. Factors which influence the incidence are: kind of serum, method of preparation of serum, quantity administered, number of injections, and the route of administration. Some type of skin rash may occur in as high as 70 per cent of patients given serum. Anaphylaxis is observed in something less than 1 per cent, and death in about 0.05 per cent (Kojis).

Mechanism. The immediate cause of the changes is a union of antigen and antibody in the tissues, and the result is a powerful stimulation for contraction of smooth muscle. The exact location of the major reaction varies with the animal species—bronchi in the guinea pig, pulmonary artery in the rabbit, and hepatic veins in the dog. In man any one or all of these may be involved. Proof of the site

of reaction in the tissues is given by the following facts: there is an incubation period of passive anaphylaxis; anaphylaxis occurs in decerebrated animals; and the smooth muscle of a sensitized guinea pig freed of blood by perfusion contracts on exposure to the homologous antigen.

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LXII

Diseases Related to Hypersensitivity: Diffuse Collagen Diseases

On the basis of anatomic studies a number of diseases were described in the last fifty years which had in common widespread involvement of blood vessels, smooth muscle, and connective tissue. In most instances the causal factors were entirely unknown. All were relatively rare and the similarities were not recognized. Among the disease entities so established were polyarteritis nodosa, disseminated lupus erythematosus, dermatomyositis, and generalized scleroderma.

In the late 1930's and early 1940's several events stimulated interest in these diseases and led to a new concept of them as a group. The most notable event was the introduction of the sulfonamides in the treatment of many diseases. It was soon recognized that the sulfonamides can produce a reaction altogether similar to that of serum sickness. It was shown that the sulfonamide combines with plasma protein to form an antigen which sensitizes the tissues anaphylactically to the sulfonamide. More importantly autopsy studies revealed lesions in those who died of hypersensitivity to sulfonamides identical with those of the disease polyarteritis nodosa (Rich). Renewed study at about the same time of the tissues in fatal serum sickness showed also lesions identical with those of polyarteritis nodosa (Rich). Experimental studies quickly confirmed in man the observations that uncomplicated anaphylactic reaction of the serum sickness type in rabbits was associated with lesions of polyarteritis nodosa (Rich and Gregory).

More intensive investigation of the anatomic lesions in the other diseases of the group indicated many similarities and identities. It is clear today that there is a group of diseases which may be produced by a prolonged anaphylactic type of hypersensitivity. It does

not follow that all similar tissue reactions have this single pathogenesis.

There is considerable evidence that rheumatic fever is a member of this group and that rheumatoid arthritis is related (Rich).

Basic Anatomic Lesions. The essential lesions of the anaphylactic type of hypersensitivity include: fibrinoid change in collagen and in ground substance, formation of cells into groups similar or identical with those of the Aschoff body in rheumatic fever, verrucous endocarditis, myocarditis, sterile serositis particularly of the pericardium, a distinctive pneumonitis, necrosis and inflammation of arteries, focal necrosis of lymph nodes and spleen, characteristic change in the glomerular capillaries, and tissue eosinophilia. Why one combination occurs in one disease or in one person and not in others is probably related to the known variable reaction of tissues and cells to a given stimulus.

The descriptions of the individual diseases which follow should be regarded as average or typical. In any given case there may be considerable deviation from the type and in some it may not be possible to classify the disease into one distinct type.

Effect of Treatment on Lesions. Cortisone and ACTH have a favorable effect on some patients. Preliminary anatomic studies suggest that these drugs induce healing (Baggenstoss, Shick, and Polley).

Disseminated Lupus Erythematosus— Atypical Verrucous Endocarditis

Since Osler first observed visceral changes in association with erythematous lesions of the skin, a number of pathologic processes have been observed and described, mostly under one of the two terms given above. Apparently they both represent the same disease,

the manifestations of which vary from case to case.

Pathologic Anatomy. Cutaneous Changes. In the skin of the face there are erythematous macules and papules, tending to be confluent, over the bridge of the nose, in the pattern of a butterfly (butterfly fever). There are similar lesions on the ends of the fingers, on the ends of the toes, on the thenar and hypothenar eminences, and on the balls of the feet. Within the erythematous areas there are frequently petechiae. In the mouth there are

and infiltration of mononuclear cells and plasma cells. In the myocardium there are small foci of necrosis of the fibers, and infiltration with polymorphonuclear leukocytes (Gross; Jarcho; Libman and Sacks).

Renal Changes. The kidneys are generally slightly larger than normal, and over the surface are many small, depressed scars, and numerous petechiae. In some glomeruli there are isolated lobules with necrosis and thrombosis. The remainder of the glomerulus shows some pathologic change. The most distinctive

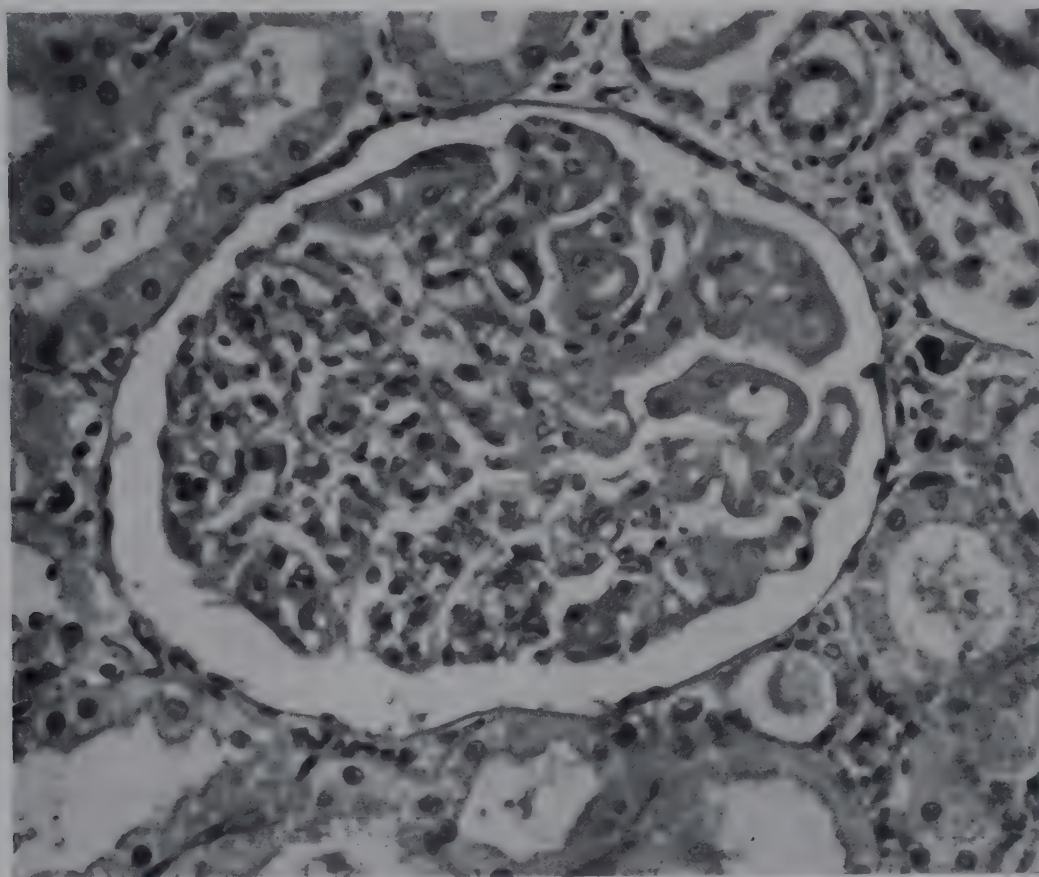


Fig. 261. Renal lesion in disseminated lupus erythematosus. (Armed Forces Institute of Pathology, Neg. No. 77765 contributed by Captain Arthur Allen.)

erythematous macules with ulceration. In older lesions there are pigmentation of the skin and telangiectasis.

Cardiac Changes. The heart is usually not enlarged. In about one-half of the cases there is a grossly characteristic type of vegetative endocarditis, known as "atypical verrucous endocarditis," or "endocarditis of the Libman-Sacks type." Any one of the valves may be involved. The vegetations are typically flat, tawny or pink, and granular, and occur at the base of the valve, particularly in the pocket beneath the posterior leaflet of the mitral valve. The vegetations are composed of granular acidophilic debris, fibrin, and mononuclear cells and lymphocytes. In the valvular rings there are fibroblastic proliferation

and change is a peculiar hyaline thickening of the basement membrane of the glomerular capillaries, known as the "wire loop" lesion of disseminated lupus. Distinctive amphophilic droplets similar to those in the L.E. cell (see below) are also observed in the glomeruli.

Membranous and Other Changes. In the serous membranes there is an acute fibrinous inflammation, or fibrous adhesions with obliteration of the cavity. In the eye there are small hemorrhages (Mauerness). The spleen is slightly to moderately enlarged. Focal necroses with basophilic bodies in the lymph nodes are observed (Ginzler and Fox). Smears of the bone marrow made during life show a distinctive and possibly pathognomonic cellular type; a large mononuclear cell

with basophilic inclusions known as the L.E. cell (Haserick and Bortz).

Vascular Changes. The vascular changes vary from simple dilatation of the capillaries with hemorrhage and transudation of fluid, through proliferative lesions of the lining endothelium of capillaries, arterioles, and venules, associated with thrombi, to conspicuous degenerative and necrotizing lesions in the walls of all vascular channels, associated with thrombosis and hemorrhage (Klemperer, Pollack, and Baehr).

Incidence. Disseminated lupus is largely a disease of women in a ratio of about 3 to 1. Many cases first appear or show exacerbation following exposure to sunlight. There are no abnormal porphyrins in the urine.

Clinicopathologic Correlation. Because of the extremely irregular distribution of lesions from patient to patient, the signs and symptoms vary greatly. As evidence of an infection, there is an irregular fever for weeks, months, or years. The hypoplasia of the bone marrow is reflected in leukopenia and anemia. The lesions in the kidney result in albuminuria, hematuria, and retention of the nitrogenous products in the blood stream. The swelling of the joints results from edema of the periarticular tissues and from the accumulation of excessive amounts of fluid within the joint cavity. The pleurisy and the pericarditis produce their usual signs. The hemorrhages and inflammation in the eye may be visible by ophthalmoscopic examination. Examination of the skin with a capillary microscope shows an unusually abundant, widely dilated capillary plexus.

Discoid Lupus Erythematosus. In its gross characteristics this lesion is identical with that of disseminated lupus. There are hyperkeratosis, keratotic plugging of the hair follicles and sweat glands, parakeratosis, acanthosis alternating with atrophy, edema of the dermis, and slight perivascular lymphocytic infiltration. The relation between discoid and disseminated lupus is not established (Montgomery).

Polyarteritis Nodosa

Since this disease is characterized by focal inflammation of all coats of the muscular arteries, the term "polyarteritis nodosa" is more exact than the original term used by Kussmaul and Maier, "periarteritis nodosa."

Pathologic Anatomy. There are small nodules attached to the vessels in all organs and tissues to a variable degree. In about 80 per cent of instances, the kidneys are involved, and, in a descending scale of frequency, the heart, liver, gastro-intestinal tract, pancreas, mesenteric arteries, skeletal muscles, peripheral nerves, and central nervous system. Infarcts in the spleen, kidneys, and myocardium are not uncommon.

The initial change in the blood vessels appears to be necrosis and edema of the media of the muscular arteries, involving the entire circumference or only a part of the wall. Deposition of fibrin and fragmentation of the elastic fibrils rapidly follow. Polymorphonuclear leukocytes migrate into the area, as well as numerous eosinophils, lymphocytes, and plasma cells. Inflammation and edema of the same variety in the adventitia soon follow. When the necrotizing and inflammatory lesion involves the intima, there are thrombi in the lumen. In healing, fibroblasts proliferate in the entire focus, which is infiltrated with many eosinophils. Scars of the walls of blood vessels, consisting of dense fibrous tissue, with some deposit of hemosiderin, apparently represent complete healing. When the healing and healed lesions of the vessels are abundant, there may be many small and large scars of the organs, representing healed infarcts (Libman). Microscopic changes in the arteries resemble those of Rocky Mountain spotted fever (Bennett and Levine).

Incidence and Causal Factors. Polyarteritis nodosa is more common in men in the ratio of 4:1, and the average age at the time of death is thirty-one years.

Clinicopathologic Correlation. The signs and symptoms of polyarteritis are extremely variable, because of the variation in the distribution of lesions. The actual nodular lesion may be clinically demonstrable in the subcutaneous tissues or in the eye. The changes caused by infection are fever, chill, prostration, and leukocytosis, sometimes with eosinophilia (Lebowich and Hunt). Interruption of the blood supply to the kidney and infarction lead to blood in the urine, and at times to the signs and symptoms of uremia. Similar changes in the heart give the typical picture of infarct of the myocardium, with cardiac failure. Involvement of the blood supply to the abdominal organs may produce the pic-

ture of mesenteric thrombosis, or of acute cholecystitis. There is pain in the abdomen and sometimes melena (Allen). Pain in the muscles and degeneration of the peripheral nerves with neuralgia are probably on the same basis (Ophüls). Rupture of vessels or of the small aneurysms may lead to serious or fatal hemorrhage.

Dermatomyositis

Pathologic Anatomy. The *gross* pathologic changes are not conspicuous. On one or more

liferation of the connective tissue of the dermis and more advanced atrophy of the epithelium. In the striated muscles, including the heart, there is diffuse and focal inflammation. The interstitial tissue is edematous and infiltrated with lymphocytes. The muscle fibers are swollen and hyalinized, and show no cross-striations. There is proliferation of the sarcolemmal sheaths, and in the advanced cases the muscle is in part or wholly replaced by fibrous tissue. The peripheral nerves show a slight inflammation in the perineurium, and degeneration of the myelin sheaths. The cen-

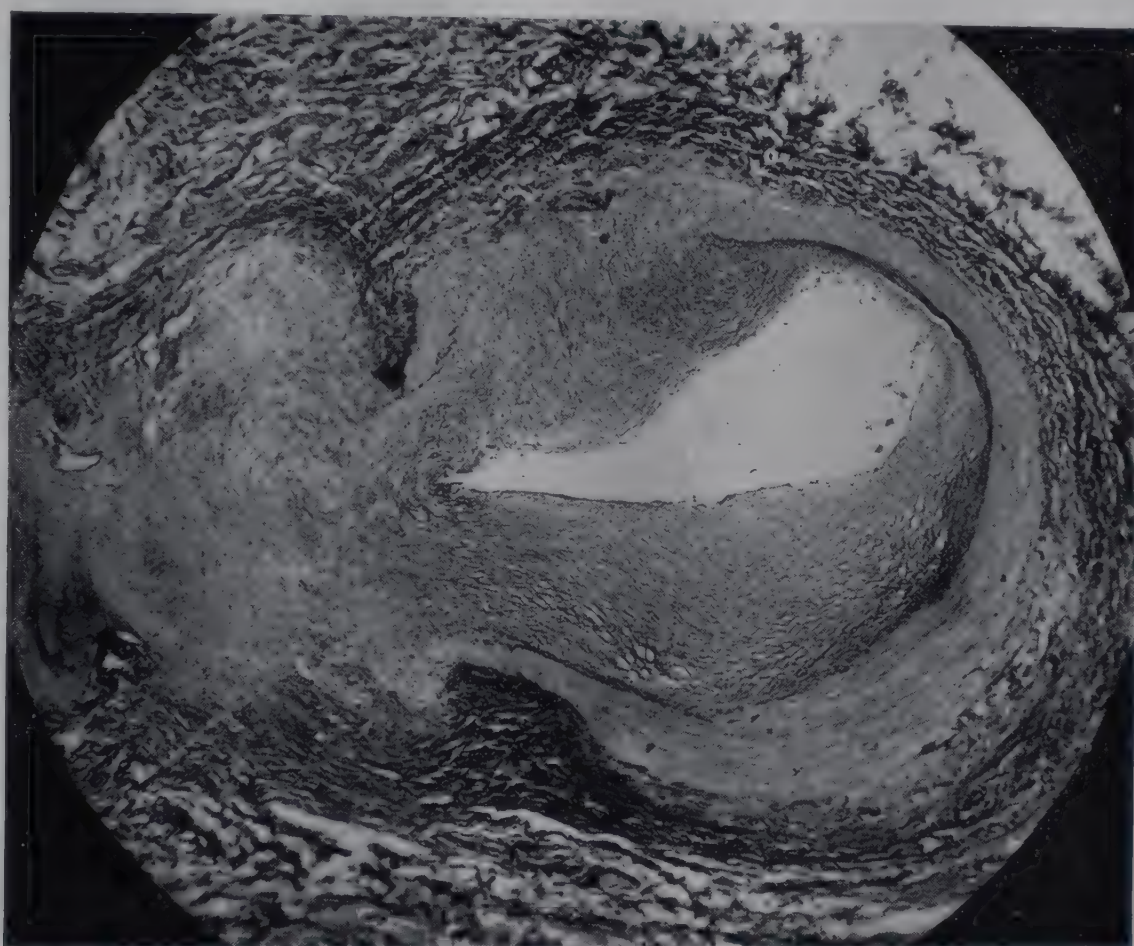


Fig. 262. Healed polyarteritis nodosa. (Nomenclature and Criteria for Diagnosis of Diseases of the Heart. New York Tuberculosis and Health Association, Inc.)

parts of the body there are irregular areas of edema and hyperemia of the skin, with occasional desquamation, formation of vesicles, and excoriations. The muscles are atrophic, pale, and at times fibrotic. The spleen is usually enlarged, and most patients have terminal bronchopneumonia.

The *microscopic* changes in the skin consist, in the early stages, of edema of the collagen, atrophy of the epidermis, hyperkeratinization, and perivascular infiltration with lymphocytes, plasma cells, and mononuclear cells. The walls of small blood vessels are thickened and hyalinized, and are occasionally necrotic. In later stages there are pro-

tral nervous system shows no pathologic changes except degeneration and loss of ganglion cells in the motor nuclei which supply the affected muscles.

Clinicopathologic Correlation. The changes in the skin produce few symptoms, but the inflammation and destruction of the skeletal muscles lead to pain and later to weakness. Involvement of the muscles of deglutition and the accessory muscles of respiration gives rise to the most outstanding symptoms, and probably plays a role in initiating the terminal bronchopneumonia. The usual symptoms of an infection—malaise, fever, and anorexia—are present in most patients. There are cre-

atinuria and a decrease in the creatine content of the muscles (Kinney and Maher).

Scleroderma

Many consider scleroderma as the chronic form of diffuse collagen disease. Because of the prominence of changes in the skin, it was for many years regarded as a skin disease. However, there are changes in all tissues and it cannot be considered a local lesion.

Pathologic Anatomy. *Changes in the Skin.* The typical lesion is a smooth, hard, and tight skin, first evident over the hands and feet, and the bridge of the nose and cheeks. There is then centripetal spread toward the trunk. The epidermis is atrophic and there is an increase of pigment. The dermis and subcutaneous tissues show predominantly diffuse fibrosis, but fibrinoid change is evident. Atrophy and cellular infiltration of skeletal muscles identical with that of dermatomyositis is observed.

Lesions in the Viscera. Diffuse and focal fibrosis of all viscera has been described, particularly in the heart (Weiss, Stead, Warren, and Bailey), esophagus (Olsen, O'Leary, and Kirklin), intestine (Bevans), lungs (Getzowa), and thyroid. The alterations in the kidney may be identical with those in disseminated lupus, including the "wire loop" lesion.

Vascular Lesions. The blood vessels show any phase of the typical change in diffuse collagen disease from necrosis to advanced perivascular fibrosis.

Incidence. Scleroderma is twice as common in women as men. The peak incidence is in the fourth and fifth decades.

Clinicopathologic Correlation. The diffuse fibrosis of the skin causes the smooth tight appearance and also limits the movement of the joints. Secondary calcification in the periarticular tissues is the basis for the nodules about the joints. Esophageal fibrosis is the reason for dysphagia, and similar lesions in the intestine are related to abdominal discomfort and obstruction. Dyspnea and other respiratory difficulty may be the result of pulmonary fibrosis or of atrophy in the respiratory muscles. The myocardial fibrosis may induce cardiac failure.

Acrosclerosis. Acrosclerosis, a disease with similar changes in the skin, is believed by some to be a distinct entity and a trophic disorder related to vasomotor disturbances (O'Leary).

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LXIII

Pneumoconiosis

During each twenty-four hours of adult life, man breathes into the lungs about 12,000 liters of air. This air contains, in addition to the needed oxygen, a variable number of particles of carbon, silica, and other particulate matter. In rural communities this particulate matter is at a minimum, but in large, modern cities the air contains appreciable amounts of carbon. In certain industries the number of particles within the atmosphere is excessive, and represents a definite hazard to the health of the employed person. In general it is believed that any dust with a concentration greater than 60,000,000 particles per cubic foot, containing 5 per cent of free silica, under 10 microns in diameter, or any dust containing 10,000,000 particles per cubic foot with 35 per cent of free silica, is dangerous.

The effect on the respiratory tract of the inspired particulate matter depends on its chemical composition, and on the amount which accumulates over the years in the lung and lymph nodes. The pathologic changes caused by particulate matter in the lung are known collectively as "pneumoconiosis."

Nonoccupational Anthracosis

Pathologic Anatomy. In urban dwellers with increasing age there is an increasing black mottling of the lung, most conspicuous in the apex, in the anterior border of the upper and lower lobes, and in the posterior border of the upper lobe. The diaphragmatic surface and the interlobar surfaces are relatively free of pigment. On careful examination, when there are moderate deposits, it may be observed that the pigmentation forms a fine tracery of lines over the pleural surface of the lung. These lines correspond to the interlobular septa, and the junctions of the lines corre-

spond to the small masses of pleural lymphoid tissue.

In some cases, particularly if the lung is emphysematous, there are diagonal bands of pigmented and unpigmented tissue. The unpigmented bands represent the surface in apposition to the ribs. It is generally supposed that this is a matter of pressure and lack of expansion, which inhibits the deposit of pigment in the latter parts of the pleura. In the parenchyma of the lung the pigment is deposited along the interlobular septa and in the adventitial tissue about the bronchi and great vessels. As on the pleural surface, there are lines, irregular in width, corresponding to lymphatic channels, and nodules where these lines join, corresponding to the intrapulmonary lymphoid tissues. The bronchial and tracheobronchial lymph nodes at the hilum of the lung are slightly increased in size and uniformly black. Early the pigment is most prominent in the medulla of the lymph nodes, but later it accumulates in the cortex as well. Unless the deposit is excessive, the nodes are firm. The pleura is usually smooth and glistening, and rarely there are adhesions resulting from the deposit of pigment in the pleura.

The greater part of the pigment is contained within large mononuclear cells, although when there are large amounts some of the pigment is free in the intercellular spaces. In association with the deposits of pigment, particularly in the lymphoid tissue, there is a slight fibrosis. Microscopic study of the small nodules which may be palpated in the substance of the lung reveals proliferation of connective tissue in the form of a whorl, indicating that this lesion is the result of silica.

Complications. In certain parts of the world, particularly in Central Europe, where there is no attempt to smoke control and the

common fuel is soft brown coal, the degree of nonoccupational anthracosis is high. For example, the deposit in the apex of the lung may be sufficient to bring about death of the tissue and the formation of a cavity, usually 2 to 4 cm. in diameter. There is no fibrous tissue capsule about the cavity, although the entire surrounding lung tissue is intensely pigmented.

Similarly the tracheobronchial lymph nodes may contain excessive deposits of pigment with resulting softening and liquefaction of the tissues. If the lymph node is in contact with a blood vessel or a bronchus, the liquefaction at times involves the wall of the hollow viscus, with discharge of the black liquid into the lumen. In the process of healing, the depressed scar remains pigmented, and may be found at autopsy many years later. On rare occasions a lymph node may simultaneously rupture into a branch of the pulmonary artery and into a bronchus, with resulting fatal hemoptysis. If the pigment is discharged into a blood vessel, the granules are carried to all parts of the body by the systemic blood stream, filtered out for the most part in the spleen and liver, and there remain for an indeterminate time. On section of the spleen a black pigment is seen in the malpighian bodies, and in the liver small pigmented nodules in the portal spaces can be observed. In most cases of anthracosis of the spleen and liver, the lymph nodes along the splenic artery are also pigmented. Direct lymphatic channels from the base of the lung may carry the pigment to the lymph nodes at the hilum of the liver and about the celiac axis.

Chemical Aspects. The degree of nonoccupational anthracosis depends upon the purity of the atmosphere of the community in which the person has lived for the greater part of his life (Taylor). In Pittsburgh in 1914 the lungs were found to contain between 1.2 and 5.3 gm. of carbon, while in Ann Arbor, Michigan, the lungs contained between 0.145 and 0.405 gm. of carbon. Similarly there are variations in the content of silica from 0.5 to 2 mg. per gram of lung tissue, with an average of 1.13 mg. (McNally). A value for silica above 2 mg. per gram of lung tissue in general indicates that the person was exposed for a period of years to an unduly dusty atmosphere.

Experimental Anthracosis. Guinea pigs and rabbits exposed to a dusty atmosphere, in which the greater part of the dust is pure car-

bon, have pathologic changes in the lung similar to those of man. The pigment enters the respiratory bronchioles and alveoli, where it is phagocytized by large mononuclear cells. These cells migrate through the wall of the respiratory bronchioles and enter the terminal branches of the lymphatic system. The superficial lymphatics drain toward the pleura, and the deeper lymphatics drain toward the hilum. The cell containing the pigment is carried to the small masses of lymphoid tissue in the pleura and to the medulla of the tracheobronchial lymph nodes. At these two points the cell is trapped and remains there until it is killed. Thus the pigment accumulates at these two points. With increasing exposure, and as the tracheobronchial and pleural lymph nodes trap larger amounts of pigment, the smaller lymph nodes within the lung become similarly affected. The presence of the pigment results in a slight fibrosis and consequent slight obstruction of the lymphatic channels.

Relation to Respiratory Diseases. *Pneumonia.* It has been claimed that persons who live in dusty communities, or who have an excessive degree of nonoccupational anthracosis, show certain defects in the resolution of pneumonic processes. The anthracosis blocks the lymphatics, which are necessary for the solution and drainage of any inflammatory exudate.

Tuberculosis. There is little objective evidence in man to relate the incidence of tuberculosis to the degree of anthracosis, although it has been suggested that the lesions of tuberculosis in anthracotic lungs are smaller and more localized than in nonanthracotic lungs. The explanation of this has been found in the blockage of the lymphatics, which prevents the spread of the disease (Haythorn). In experimental animals, with a relative nonvirulent bacillus, a moderate degree of anthracosis confers some slight protection against tuberculosis. With virulent bacilli anthracosis has no demonstrable effect on the origin or progress of tuberculosis (Gardner, Cummings, and Dowd).

Occupational Anthracosis (Bituminosis). In the coal mines of the soft coal industry, there is an excessive degree of anthracosis of the lung, but there is a sufficient amount of silica in the coal and in the associated rocks to place this pathologic change in the group of modified silicoses. It will be discussed under that title.

Silicosis

Silicosis may be divided into two types: modified silicosis and pure or uncomplicated silicosis. By *modified silicosis* is meant the disease produced by dust containing other particulate matter, such as carbon (anthracosilicosis), iron (siderosilicosis), calcium (calcicosilicosis), and others. *Uncomplicated silicosis* may be classified as acute or chronic. In the acute cases the lesions develop and produce death within from one to four years, while in the chronic type there is frequently

which there are deposited a few granules of pigment (Fig. 263). It is sharply outlined, and at the periphery there may be a few lymphocytes. The center of the nodule is not infrequently granular and devoid of fibrillar structure. The crystalline silica is easily identified with polarized light.

Acute Silicosis. In acute silicosis the gross pathologic changes are relatively inconspicuous. The lungs are voluminous and generally firm, but in many cases no definite nodules are palpable. With a hand lens or microscope innumerable small nodules, less than 0.5 mm.

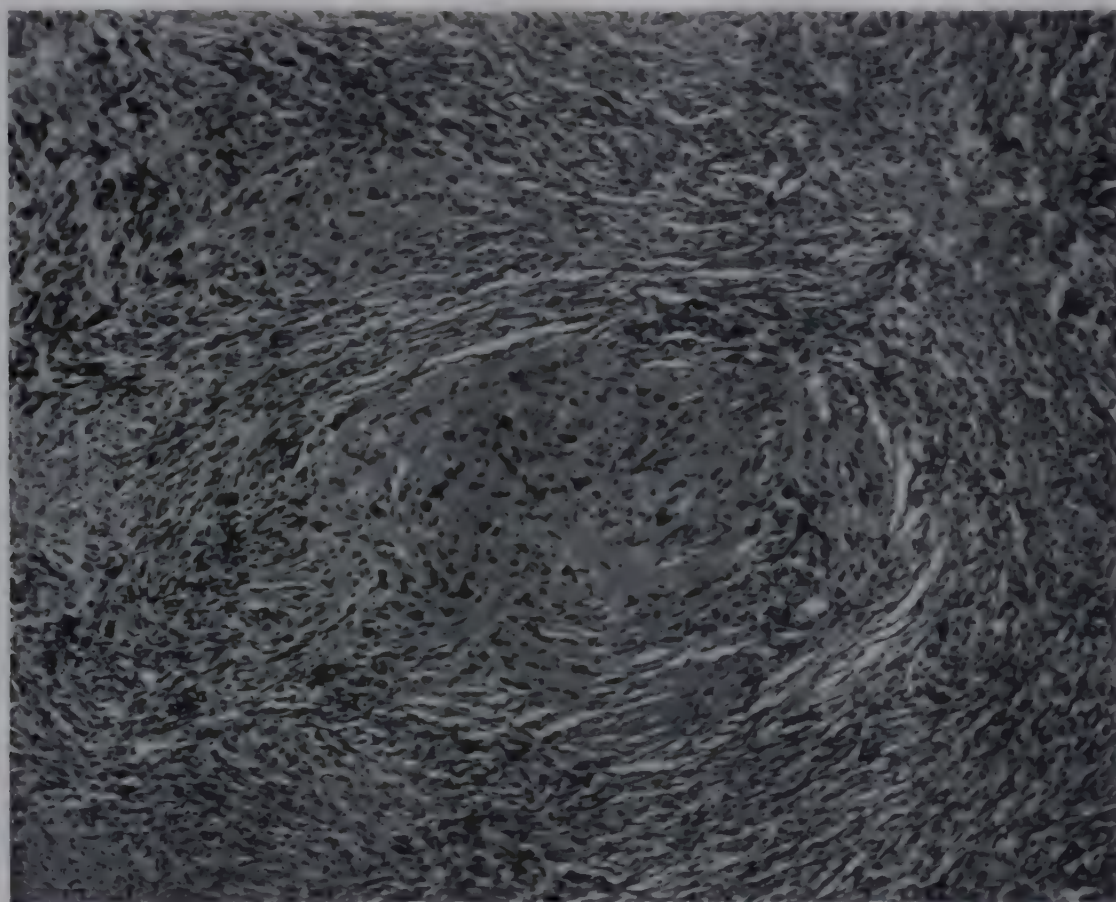


Fig. 263. Silicotic nodule in lung.

a history of occupational exposure for from ten to twenty-five years.

Chronic Silicosis. In chronic silicosis the lungs are voluminous, and do not collapse when the thoracic cavity is opened. There are dense pleural adhesions, and the greater part of the pleural cavity is obliterated. The visceral pleura is thickened, with hyalinized connective tissue. Throughout the lung there are numerous small, firm, grayish white, spherical nodules, 1 to 3 mm. in diameter. At times these nodules are more abundant and slightly larger in the upper lobes than in the lower lobes (Fig. 264). The intervening pulmonary tissue is firm, but the architecture is preserved. There are similar nodules in the tracheobronchial lymph nodes. The nodule is composed of a whorl of hyalinized connective tissue, in

in diameter, are seen throughout all parts of the lung, particularly just beneath the pleura, and forming a band contiguous to the interlobular septa. The nodules are similar in microscopic appearance to those in chronic silicosis, and differ only in size (Ritterhoff).

Experimental Production. When a particle of silica, usually less than 2 microns in diameter, gains entrance to the alveoli of the lung, it is immediately phagocytized by a mononuclear cell. These cells, when supravitaly stained, exhibit the distribution of granules and a rosette similar to that of the monocytic type of macrophage. A few of the cells are of the clasmotocytic type. These phagocytes, with the ingested silica particle, migrate through the lymphatic system to the tracheobronchial lymph nodes. The ingested silica is

toxic, and the cell soon dies and the cytoplasm undergoes autolysis. The necrotic tissue attracts a few polymorphonuclear leukocytes, and other mononuclear cells take up the liberated silica particles. In general the particles within the lymph nodes are accumulated in the form of small nodules, and the mononuclear cells at this stage demonstrate some of the properties of epithelioid cells; thus, with supravital staining there are enlarged rosettes

over the surface of these latter cells, but not over the surface of the monocytes and epithelioid cells. There is thus formed a small, spherical nodule composed essentially of monocytes, which either fuse to form giant cells, or differentiate into epithelioid cells and fibroblasts.

In from sixty to ninety days the fibroblasts, with abundant collagen between them, are the most prominent part of the nodule. Most of the

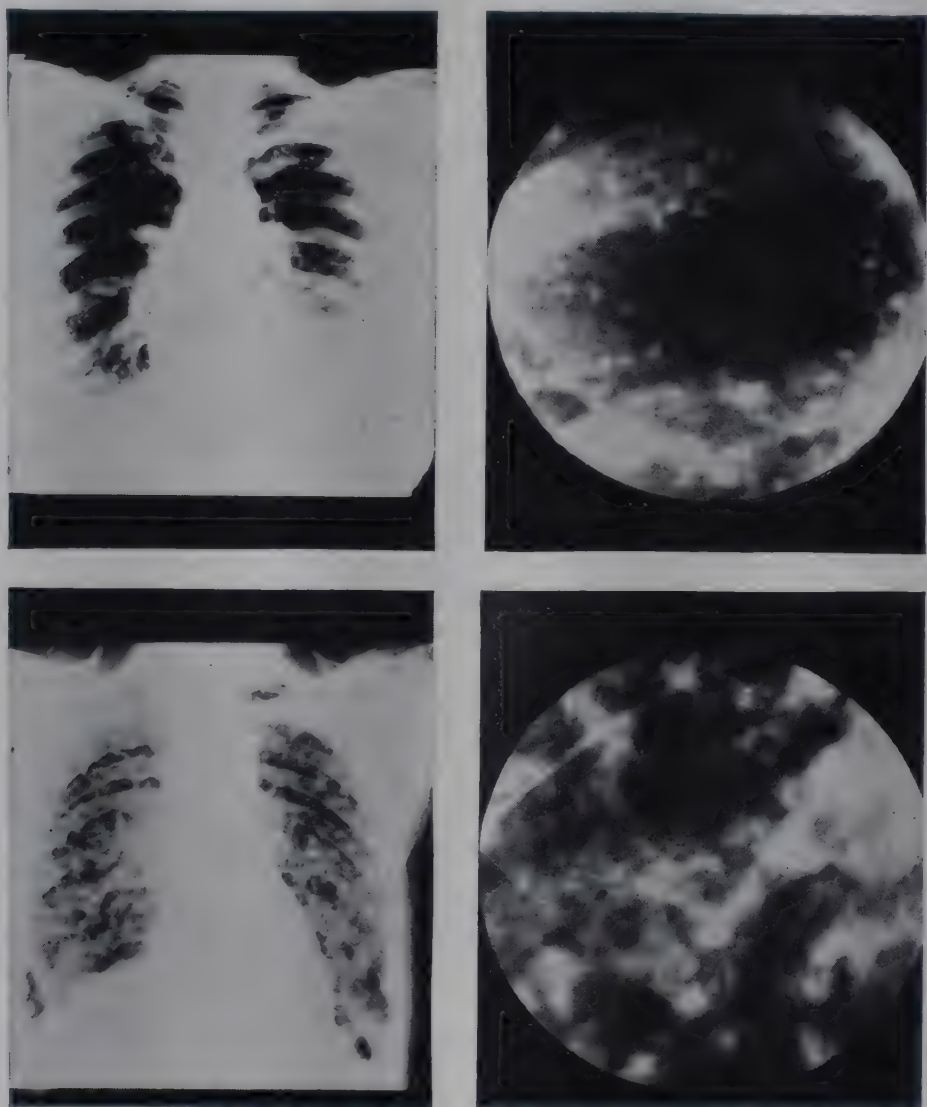


Fig. 264. Radiographic appearance of the lungs in silicosis. At the top an early stage, and at the bottom a late stage. On the left the entire thorax, and on right enlargement of a small field. (Photographs by courtesy of Dr. Edwin Ernst.)

of finely granular neutral red and scattered small particles of lipid material.

Either within the lung or in the tracheo-bronchial lymph nodes giant cells are formed, with eight to ten peripherally arranged nuclei, and within the cytoplasm a large rosette of neutral red granules can be demonstrated. Within about two months after the inhalation of silica, round or spindle-shaped cells appear within the nodule. These cells are seen to contain a few scattered droplets of neutral red with supravital staining, and are interpreted as the beginning of a fibroblastic proliferation. With silver stains there is a delicate reticulum

monocytes and epithelioid cells have disappeared, and the particles of silica are free between the fibrils of collagen. If the deposit of silica is excessive, the central part of the nodule undergoes coagulation necrosis, with the liberation of a small amount of fat (Gardner).

When silica is introduced into the lungs of rabbits, a large amount of phospholipid is freed in the tissues. This phospholipid is in general similar to that in the tubercle bacillus. This may explain the similarity of the tubercle and the silicotic nodule (Fallon). It is possible that sarcoidosis is a similar condition.

Modified Silicosis

Anthracosilicosis. The usual picture of occupational anthracosilicosis, as seen in the anthracite miners of Pennsylvania, is a type of lesion called "massive conglomerate fibrosis of the lung." The entire lung, more especially the upper lobes, is firm and rubbery, blue-black, and completely devoid of normal architecture. In the less affected parts and along the anterior border the small amount of remaining pulmonary tissue is emphysematous. The pleura is thickened, and the pleural cavity is obliterated by dense fibrous adhesions. The tracheobronchial lymph nodes are enlarged and similar in consistency and color to the lung. Microscopically, a diffuse fibrosis of the lung on a background of nodules is seen. Within the fibrous tissue and the nodules there are large amounts of black granular pigment. With polarized light or by chemical examination excessive amounts of silica can be demonstrated. The smaller blood vessels within the fibrous tissue show a thickening of the intima and reduction in the size of the lumen, often to complete obliteration.

In the great majority of cases there is an associated pneumonia or tuberculosis, and it is difficult to determine the exact part played by silica and by infection in the production of the massive fibrosis. It is probable that these patients suffer from repeated attacks of bronchitis and bronchopneumonia, which undergo organization, with gradual destruction and obliteration of the lung tissue.

Siderosilicosis. In miners of iron ore with an appreciable silica content, the lungs show a characteristic picture. They are rusty-red, with concentration of the pigment in small nodules corresponding to the lobules of the lung. Throughout the lung there are the typical grayish white nodules of uncomplicated silicosis. The pleural cavity is obliterated by fibrous adhesions. Microscopically, diffuse fibrosis is seen in addition to the whorled nodules. Within the fibrous tissue there is a large amount of a brown granular pigment, which stains for iron by the Prussian blue reaction. The intima of the medium-sized and small blood vessels is thickened and contains a moderate amount of the brown pigment. The lymph nodes are red and fibrotic. The silica content of these lungs varies from 1 to 2.96 per cent of dry tissue. In most instances there

is an associated tuberculosis (Stewart and Faulds).

Other Forms of Modified Silicosis. There are many minerals which contain significant amounts of silica, varying from 10 to 80 per cent. Variable degrees of silicosis and calciosilicosis are observed in workers in quartz, marble, granite, cement, and talc. Of particular interest is carborundum (silicon carbide), which contains no free silica, but does produce a mild degree of pneumoconiosis (Gardner, Durkan, Brumfiel, and Sampson). Pulmonary lesions have been described after the inhalation of the fiber of sugar cane—bagassosis (Castleden and Hamilton-Paterson).

Asbestosis

The pathologic changes of asbestosis are caused by either Canadian asbestos, known as "chrysolite," or South African asbestos, known as "crocidolite." Both contain about 50 per cent of silicon in the form of hydrated silicates.

Pathologic Anatomy. The pleura is thickened and the cavity is obliterated by fibrous adhesions, particularly over the lower lobe of the lung. The lung tissue is firm and irregularly nodular. It cuts with increased resistance, and on the cut section the individual lobules of the lung project above the surface as grayish white or blue, firm nodules. In the lower lobe these nodules are likely to become confluent, while they remain discrete in the upper lobe. In the greater part of each nodule, which is a lobule of the lung, no pulmonary architecture is discernible. The trachea and bronchi are usually the seat of a moderate bronchitis. The tracheobronchial lymph nodes are slightly enlarged, and contain small nodules similar to those in the lung.

The outstanding feature is a diffuse fibrosis of the lung, concentrated for the greater part about the respiratory bronchioles. The surrounding alveoli are collapsed and lined by cuboidal epithelium. The alveolar walls are thickened by fibrosis. Within the fibrous tissue there are the characteristic asbestosis bodies (Fig. 265). These consist essentially of a brown, branching or nodular, linear structure, usually 5 to 10 microns in width and 100 to 200 microns in length (Stewart and Haddow). With the Prussian blue reaction they stain as does free iron. About the asbes-

osis bodies there are occasional multinucleated giant cells of the foreign body type. Within the lymph nodes there is slight to moderate fibrosis, but asbestosis bodies are not formed (Gloyne).

Pathogenesis. The long asbestos fibers gain entrance to the lower respiratory tract and lodge in the respiratory bronchiole. Because of the presence of a foreign body, and probably also because of the specific action of the silicates within the asbestos, there is an exudation of fluid and cells. Within a few days or weeks there is beginning proliferation of

cally susceptible to the soluble products of asbestos, or that the constant movement of the lung leads to trauma of the bronchiolar walls by the asbestos fiber (Gardner and Cummings).

Beryllium Pneumoconiosis

Exposure to the dust or fumes of beryllium will lead to definite changes in the lungs and introduction of the metal into the subcutaneous tissue will produce a characteristic granulomatous reaction.

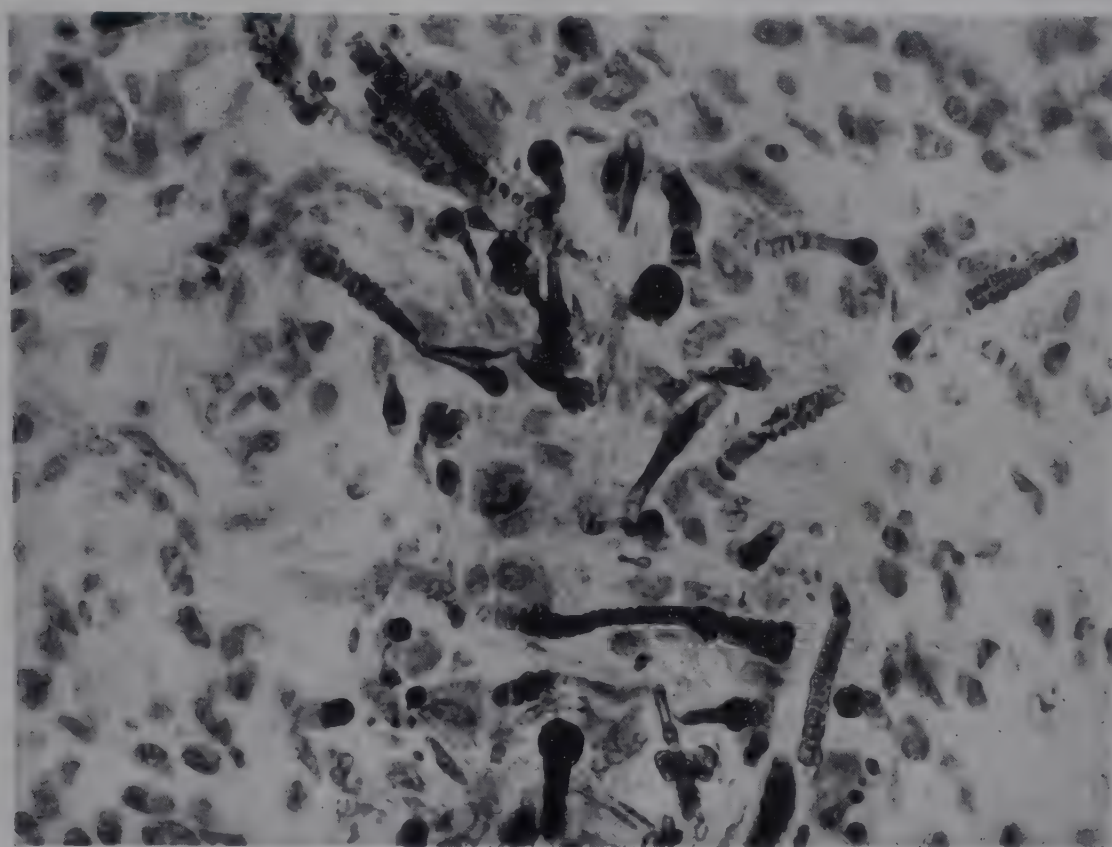


Fig. 265. Asbestosis bodies in lung.

fibrous tissue in the wall of the respiratory bronchiole. During this same period proteins and iron in the exudate are deposited upon the surface of the asbestos fiber and produce the asbestosis body. Foreign body giant cells accumulate about the fibers.

All of these changes lead to obstruction of the respiratory bronchioles with consequent collapse of the surrounding alveoli and fibrosis of the alveolar walls. The alveoli are lined by a cuboidal type of epithelium. Few of the asbestos fibers are in the lymph stream, and consequently there is little change in the lymph nodes, but the fibrosis about the bronchioles may lead to fibrosis of the lymphatic vessels, and stasis of lymph.

It is of considerable interest that asbestos produces pathologic lesions only in the lung. It has been suggested that the lung is specifi-

Pathologic Anatomy. Lesions of the lung may be observed in an acute or chronic phase or in all gradations between the two. In the acute phase the lungs are large, heavy, and inelastic. The cut surface is a homogenous pinkish gray or bluish gray. The tracheobronchial nodes are enlarged and soft. The alveoli are filled with fluid and mononuclear cells with a few lymphocytes and plasma cells. Multinucleated cells are common. At later stages there is organization of the exudate concentrically so that a central mass of eosinophilic debris remains. The alveolar walls are infiltrated with lymphocytes and plasma cells, and there is proliferation of fibrous tissue.

In the chronic phase the lungs vary in weight from 1500 to 2000 gm. Throughout all lobes there are small nodules up to 2 mm. in diameter. The intervening parenchyma is

emphysematous. There is fibrosis of the septa and of the peritruncal tissues. The alveolar walls are thickened and infiltrated with lymphocytes and plasma cells. The characteristic granuloma consists of a peripheral layer of loose connective tissue surrounding a central mass of necrotic granular eosinophilic debris similar to fibrinoid, or a Langhans' giant cell. Throughout both parts are a moderate number of lymphocytes and mononuclear cells. Similar lesions may be present in the regional lymph nodes. Changes in other viscera are rare (Dutra).

The lesion in the subcutaneous tissue is identical with the pulmonary granuloma.

Chemical Aspects. The lungs contain definite amounts of beryllium and in most patients beryllium is excreted in the urine (Dutra, Cholak, and Hubbard).

Clinicopathologic Correlation. Both occupational and nonoccupational cases are observed, the latter in persons living near a beryllium industry.

Bauxite-Fume Pneumoconiosis

In some individuals engaged in the manufacture of alumina abrasives, a lesion of the lung develops, apparently in relation to inhalation of fumes produced by fusion of bauxite.

There are a diffuse non-nodular interstitial fibrosis with mononuclear infiltration and emphysema. The bronchioles are dilated and in some there is squamous metaplasia. Arterial walls are thickened. The lymph nodes may be slightly fibrotic.

Chemical analysis of the lung reveals up to 40 per cent of the ash as alumina (Wyatt and Riddell).

Clinicopathologic Correlation and Relation of Pneumoconiosis to Other Diseases of the Respiratory Tract

The clinical signs and symptoms of pneumoconiosis are dependent upon two factors: fibrosis and obliteration of pulmonary tissue, and associated infection of the respiratory tract. The gradual destruction and fibrosis of alveoli and bronchioles lead to dyspnea, and this is probably the only symptom directly caused by the pneumoconiosis. Other symptoms, and in many instances the incapacitation, result from chronic bronchitis, pneumonia and tuberculosis.

Chronic Bronchitis. In most cases of pneumoconiosis the mucosa of the bronchi is swollen, red and covered with a quantity of mucus, resulting in a persistent productive cough.

Pneumonia. In most pneumoconioses there is fibrosis of the lymphatics and consequent lymph stasis. It has been suggested, and in part proved, that this blockage of the lymphatics leads to inadequate resolution of a pneumonic exudate, so that the incidence of unresolved pneumonia is higher in persons with pneumoconiosis. This is supported by the observation that a part of the pathologic process in severe anthracosilicosis would appear to be the organization and fibrosis dependent upon repeated attacks of bronchopneumonia. The old theory that the incidence of pneumonia was higher in persons with silicosis than in others has been conclusively disproved.

Tuberculosis. Miners' phthisis has been known since the earliest days of man's activity in underground mines. It is only in the last few decades that this has been recognized not as a simple pneumoconiosis but as pneumoconiosis plus active pulmonary tuberculosis. From 60 to 70 per cent of all patients with silicosis or modified silicosis die of pulmonary tuberculosis. The reason for this close association of the two diseases is seen in studies on experimental animals. In a rabbit inoculated with the R-1 strain of the tubercle bacillus, the lesions are usually healed within a period of four to six months. If a rabbit is exposed to silica dust either before or after the inoculation with the R-1 strain of the tubercle bacillus, progressive fatal tuberculosis develops (Gardner). Silica added to cultures of the tubercle bacillus enhances the growth of the organism, and silica injected into the subcutaneous tissues of rabbits serves as a focus for the active growth of the tubercle bacilli (Kettle).

Carcinoma of the Bronchus. The relation of pneumoconiosis to carcinoma of the bronchus is discussed fully under "Causal Factors in Carcinoma of the Bronchus," p. 696.

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LXIV

Diseases Caused by Poisonous Gases

The atmosphere contains about 21 per cent oxygen, 0.04 per cent carbon dioxide, and 79 per cent inert gases—nitrogen, helium, xenon, krypton, neon, and argon. Any significant decrease of the oxygen, either absolute or

tions of over 0.02 to 0.05 per cent by volume. In fatal poisoning the blood contains from 30 to 75 per cent, depending on the concentration in the inspired air, the duration of exposure, and the rate and depth of respiration

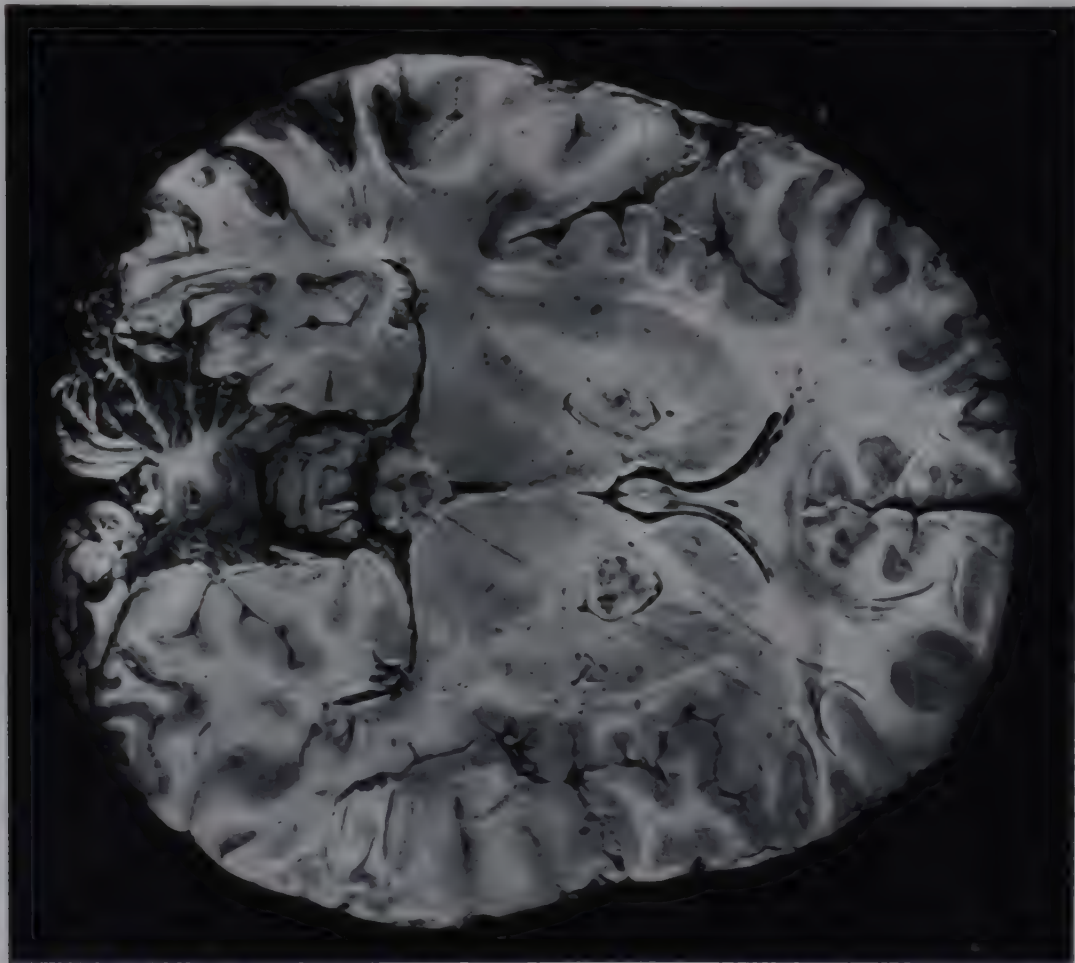


Fig. 266. Hemorrhage and necrosis in basal ganglia following poisoning with carbon monoxide.

relative, results in asphyxia. Similarly, a relative or absolute increase of carbon dioxide leads to untoward effects or even death. Of equal or greater importance than variation in the normal constituents is the presence of poisonous gases in the atmosphere. Carbon monoxide and the war gases are the most important of these.

Carbon Monoxide Poisoning

Carbon monoxide is an odorless, colorless gas, dangerous to human life in concentra-

Pathologic Anatomy. The firm union of carbon monoxide with hemoglobin decreases the oxygen-carrying capacity of the blood, and anoxia ensues, with resulting hyperemia and edema of the viscera, petechiae and ecchymoses in the serous and mucous membranes, and foci of hemorrhage and necrosis in the globus pallidus and putamen of the brain. The cerebral lesion appears after two to three days. It is believed to be the result of anoxia in a part of the brain poorly vascularized, but it may be a direct toxic effect of carbon monoxide. The bright, cherry-red color of

the blood and tissues is the characteristic color of carboxyhemoglobin.

Occurrence. Acute carbon monoxide poisoning is seen under conditions in which there is incomplete combustion of carbon in a closed space, and in homicide or suicide with illuminating gas. Intoxication with alcohol is frequently the factor that permits people to expose themselves unknowingly in closed rooms with poorly regulated stoves. Carbon monoxide poisoning is also a factor in the fatalities incident to modern aerial bombing. Carbon monoxide poisoning is seen also in workers in petroleum, and about blast furnaces (Public Health Reports).

Chronic Carbon Monoxide Poisoning. The blood of taxi-drivers in large cities may contain as much as 6 per cent carboxyhemoglobin. Some persons exposed to carbon monoxide day after day develop polycythemia, and occasionally there are irreversible changes of hypoplasia of the bone marrow, fatty degeneration of the viscera, and degeneration of the ganglion cells of the brain.

Miscellaneous Poisonous Gases of Civilian Life—Chemical Pneumonia

Poisonous gases occasionally encountered in civilian life include hydrogen sulfide, sulfur dioxide (Goldburgh and Gouley), nitrous oxide, nitric oxide, nitrogen dioxide, and ammonia. In addition to simple displacement of oxygen and consequent asphyxia, some of these have specific systemic effects. All are powerful irritants to the respiratory tract; and if a person exposed survives, "chemical pneumonia" results.

Chemical Pneumonia. Within four to twenty-four hours after exposure to a poisonous gas, there is inflammation in the bronchi and in the lungs, characterized early by massive edema, and later by immigration of cells and deposition of fibrin. The bronchial and alveolar epithelium is desquamated. In the process of repair, regenerated epithelium forms large syncytial masses with multiple nuclei. The fluid not infrequently coagulates on the alveolar wall to form a hyaline membrane. Secondary bacterial infection may appear after several days.

Poisonous Gases Used in Warfare

Poisonous gas as a weapon of warfare was first used by the Imperial German Army at

Ypres against French and Canadian troops on April 2, 1915, when 168 tons of chlorine was carried by the wind into the Allied positions on a front of six kilometers. There were 15,000 casualties and 5000 deaths.

Types of Gas. Five general types of war gases have been developed: tear gases, vomiting gases, choking gases, blister gases, and blood and nerve poisons. The *tear gases* are harmless to the body as a whole, but bring about a temporary inflammation of the eyes, so that the troops are incapacitated for a long or short period. The *vomiting gases* produce a similar transient inflammation and irritation of the nose and pharynx. The inhalation of either of these types of gas makes the wearing of a gas mask uncomfortable, and is apt to cause the person to remove the mask and thus be subject to the effects of the more dangerous and lethal gases. The *blood and nerve poisons* are those generally recognized in civilian life, notably hydrocyanic acid and carbon monoxide. The *choking gases* and the *blister gases* are discussed separately.

Pathologic Anatomy. It is difficult to evaluate the pathologic changes caused by one particular gas. Most gas attacks during World War I were made with a combination or a series of gases, and one must turn to the experimental method to analyze and separate the individual effects.

Lung Irritants or Choking Gases. The more important of these are chlorine and phosgene. A dusky, livid hue to the lips, ears, fingers, and dependent parts of the body is seen. Thin, blood-stained fluid issues from the mouth and nostrils. The lungs are bulky and completely fill the pleural cavities. The pleural cavities contain several hundred cubic centimeters of blood-tinged serous fluid, and there are frequently petechiae over the surface of the pleura. The color is variegated, with alternating foci of pale pink emphysema and dark red or blue patches of atelectasis, hemorrhagic edema, or bronchopneumonia. The interlobular septa are wide and translucent. The trachea and bronchi are completely or partially filled with a pink frothy fluid, and the mucosa is pink or dark red, without ulceration or membrane formation. If death does not occur for several days after exposure, there are usually typical foci of discrete or confluent bronchopneumonia. The heart is dilated, especially on the right side, and there

are petechiae in the pericardium, in the sheaths of the great vessels, and in the mucosa of the gastro-intestinal tract. During the first few hours or days the alveoli and smaller bronchioles are filled with an eosinophilic granular material, free from fibrin. The capillaries are hyperemic and tortuous. Within the smaller blood vessels there may be thrombi composed of platelets or red cells or of all the usual constituents of a thrombus. With the passage of days there is immigration of leukocytes and desquamation of the epithelium of the alveoli and bronchi. The lymphatics of the lung are distended with thrombi of fibrin. In most fatal cases, if the patient lives from two to four days, there is likely to be a true bronchopneumonia, with large numbers of bacteria.

Vesicants or Blister Gases. The more important of the vesicants are mustard gas and lewisite. The significant pathologic changes are in the skin and the respiratory tract, and death usually occurs from five to twenty days after exposure. The essential lesions in the skin are edema of the corium, formation of vesicles within the epithelium or between the epidermis and dermis, and necrosis of the epidermis and at times of the dermis. The vesicles are filled with a fluid containing fibrin and polymorphonuclear leukocytes. In the respiratory tract there is a fibrinous and necrotizing inflammation involving the pharynx, larynx, trachea, bronchi, and pulmonary alveoli. The lungs are voluminous. There may be a fibrinous pleurisy. Throughout the lung, especially about the smaller bronchi, roughly circular foci of atelectasis and hemorrhage occur. The bronchi are filled with a fibrinopurulent exudate, and the mucosa, if it is visible, is velvety and deep purple. The superficial layers of the mucosa are necrotic, and in severe injury the necrosis extends down to the plates of cartilage. Blood vessels are dilated, and there is infiltration with numerous polymorphonuclear leukocytes. Within the alveoli are hem-

orrhage, edema, and small or large foci of bronchopneumonia.

With the beginning of recovery, on the sixth to the eighth day, there is organization of much of the exudate, both within the alveoli and within the bronchi. There is regeneration of the epithelium of the bronchi, largely from the deeper glands, and this regenerated epithelium is frequently of the stratified variety and devoid of cilia. Many bronchi are completely obliterated, and in others there is severe stenosis of the lumen.

Clinicopathologic Correlation. The signs and symptoms are those of an embarrassment of external respiration: dyspnea, cyanosis, cough, and tachycardia.

The ultimate fate of the soldier who has been exposed to gas has been both a medical and a social problem in the United States since 1918. It is said by some that these persons are more likely to develop chronic infections of the respiratory tract and of the lungs, especially tuberculosis, than other persons. There is little objective scientific support for these statements. In fact during the five-year period immediately after 1918 the mortality rate from tuberculosis among 3000 gas casualties was lower than in the general population.

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LXV

Diseases Caused by Ingestion of or Contact with Plants or Plant Products

Many plants contain powerful principles with biological activity or toxicity. The majority have been used as medicinal plants. Chemical constituents that are responsible for the specific effects of plants may be classified in five groups: (1) amines and alkaloids, (2) glucosides, (3) essential oils, (4) toxalbumins, and (5) resins.

In the present chapter the discussion will be confined to those plants not ordinarily used as therapeutic agents, but with which man occasionally comes in contact, or ingests accidentally. In human pathology this is not an important field, but in veterinary medicine it is of extreme importance. In the states of Montana and Colorado alone the average animal loss in cattle from the ingestion of poisonous plants is estimated at \$200,000,000.

Marihuana. The flowering tops of the hemp plants, *Cannabis americana* and *Cannabis sativa*, are used as the basis for cigarettes in many parts of the world, under the names "marihuana," "hashish," "reefers," etc. Acute intoxication characterized by emotional changes results from smoking these cigarettes. There are few if any fatalities, and the nature of the pathologic changes in the tissue is unknown. After long-continued use of marihuana there is mental deterioration, but again, precise pathologic studies have not been made (Bromberg).

Milk Sickness. Milk sickness in man results from the ingestion of the milk of cows which have fed on certain poisonous plants, and themselves are suffering from the condition designated as "trembles." In the eastern United States the plant is the white snakeroot (*Eupatorium rugosum*) and in the western United States the rayless goldenrod (*Aplopappus heterophyllus*). Pathologic changes are

extreme fatty degeneration of the viscera, especially of the liver, and petechiae and ecchymoses in all tissues (Jordan and Harris). Symptoms appear two to ten days after the ingestion of the toxic milk. The mortality is about 10 per cent. The actual toxic substance is tremetol (Couch).

Akee Poisoning. Vomiting sickness of Jamaica or akee poisoning is a common, often fatal, disease in the West Indies, caused by eating the unripe fruit of the akee plant (*Blighia sapida*). At autopsy there are an intense congestion of all the viscera, petechiae and ecchymoses in many tissues, fatty degeneration of the liver and kidneys, and necrosis of the parenchymal cells of the liver, kidney, and pancreas (Jordan and Burrows).

Favism. There is an old Latin proverb "Pythagorei faba se abstinerunt," indicating that the ancient Romans recognized the danger from ingestion of broadbeans (*Vicia faba*). Within a few days after ingestion there is an acute hemolytic anemia that responds promptly to transfusions. In the bone marrow during the early stages there is suppression of erythropoiesis, and no nucleated red cells are demonstrable. The myeloid cells are hyperplastic, and there are numerous eosinophils in the bone marrow as well as in the blood stream. Megakaryocytes are also abundant. During the period of recovery the microscopic appearance of the bone marrow is gradually restored to normal.

Mushroom Poisoning. The pathologic changes in mushroom poisoning are definite but not characteristic. There are cloudy swelling, fatty degeneration, and even necrosis of the liver and kidney. Hemoglobin casts appear in the renal tubules. The ganglion cells of the brain show necrosis and fatty degeneration.

Although there are numerous poisonous mushrooms, over 90 per cent of the deaths are caused by one species, *Amanita phalloides*. Abdominal pain, nausea, vomiting, and diarrhea come on six to fifteen hours after ingestion. The hepatic damage may result in clinical jaundice, and the renal changes are usually associated with oliguria and albuminuria (Vander Veer and Farley).

Dermatitis Venenata. There are over 100 plants in the United States that produce irritation on contact with the skin. Best known of these is poison ivy (*Rhus toxicodendron*). In addition there are many chemical substances included in hair dyes, hair tonics, and cosmetics, and used in industry, that cause similar changes in the skin. These conditions are known collectively as "dermatitis venenata" or "contact dermatitis" (Weber). The field is so large that it will be possible to discuss here only a few examples.

Rhus Dermatitis. The typical changes of dermatitis from *Rhus* are inflammation of the dermis and the formation of intra-epidermal vesicles. In the dermis there are infiltration of lymphocytes, moderate dilatation of the vessels, and edema of the tissues. Rarely, the vesicles become pustules by infiltration with polymorphonuclear leukocytes. The lesions appear in from a few hours to several days after exposure, and subside gradually. In a rare person, following a single exposure, a paroxysmal or continuous eczema or papular eruption may persist for months or years.

The active principle of *Rhus* may be extracted with fat solvents and injected intramuscularly as an immunizing agent to increase the resistance of a susceptible person (Spain and Cooke; Caulfield). Animals sensitized to poison ivy are also sensitive to poison oak, indicating the identity of the two antigenic principles (Straus).

Pollens responsible for the various forms of hay fever may induce dermatitis on contact with the skin. The lesion is due not to the

specific atopen, but to an essential oil similar to that of *Rhus* (Brown, Milford, and Coca).

Miscellaneous Poisonous Plants. In India a form of epidemic dropsy is believed by some to be caused by an essential oil of the mustard seed, possibly allylisothiocyanate. Similar changes may follow the excessive use of the oil of the seed of the Mexican poppy (*Argemone mexicana*). Eating of the pods, fruits, or beans of the plant *Pithecellobium geminum* in the Dutch East Indies leads to a condition known as "gengkol poisoning." There is excessive damage to the kidney, with albuminuria and red blood cells in the urine.

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LXVI

Diseases Caused by Organic Substances—Untoward Effects of Therapeutic Agents

A poison is a substance which when introduced into the body in relatively small quantity, and acting chemically, is capable of producing death or serious injury to health in the ordinary person in average health.

Classification of Poisons. Poisons may be classified by their action into corrosives, irritants, and neurotics; or on the basis of their chemical nature into (1) gaseous poisons, (2) organic poisons, (3) inorganic poisons, and (4) food poisons. The latter classification is used here. Food poisons have been discussed in Chapter XXXIII, p. 279, and gaseous poisons in Chapter LXIV, p. 520. In this chapter and in the next the effects of the more important organic and inorganic poisons will be outlined.

Manifestly it is only possible to discuss a few of the many substances. An attempt is made to include those seen frequently or in a general practice. The reader is referred to textbooks of toxicology for details.

Liquid Petrolatum

Histologic and chemical studies of the wall of the intestine, of the mesenteric lymph nodes, of the liver, and of the spleen give definite evidence that a small amount of liquid petrolatum is absorbed after oral administration. Histologic sections of the intestine show intracellular and extracellular droplets of oil in the tunica propria. There is no associated fibrosis, and there are no giant cells. In the mesenteric lymph nodes there are large droplets of fat but again without any tissue reaction about them. In the liver and in the spleen the oil collects within the phagocytic cells (Stryker). There is no evidence that the deposit of oil within the intestines or in other tissues interferes in any way with the physio-

logic functions of these organs. There is, however, clear evidence that there is interference with the absorption of vitamin A (Curtis and Kline).

Parenterally Injected Oil

Many drugs used today are dissolved in vegetable oils, notably sesame oil. In some persons painful and disabling masses of inflammatory tissue result after injection of these into the subcutaneous tissue. Fibrosis, foreign body giant cells, and mononuclear cells filled with fat are seen microscopically. Progressive growth results from the migration of fat into the surrounding tissue (Conrad, Conrad, and Weiss). Injected paraffin, formerly used to block a hernial orifice or for cosmetic purposes, incites a foreign body reaction and slight fibrosis.

Iodized oil used intrathecally to demonstrate the subarachnoidal space induces the formation of the fibrinous adhesions about the lower part of the spinal cord (Marcovich, Walker, and Jessico). Iodized poppyseed oil employed in the visualization of the bronchi is apparently gradually absorbed without permanent damage to the pulmonary tissue.

Lipoid Pneumonia

Within the past decade it has become evident that the use of oily nose-drops is often a dangerous therapeutic procedure (Cannon and Walsh). The oil runs along the mucosa of the pharynx and enters the lung, where it provokes an inflammatory reaction. The aspiration of cream or cod-liver oil by infants produces the same general type of pathologic reaction. Some aspirated oils cause an acute inflammatory reaction, and others cause either

no reaction or a chronic proliferative type of inflammation.

Lipoid Pneumonia Caused by Oils Producing Acute Inflammation. Throughout the lung there are small or large, single or confluent, roughly spherical nodules of firm tissue. The area is elevated above the surface of the surrounding lung, the architecture of the lung is partially obscured, and the tissue is distinctly yellow. In the yellow foci the alveoli are distended with polymorphonuclear leukocytes, a small amount of fibrin, and a large number of mononuclear cells filled with vacu-

Throughout the thickened alveolar septa is a moderate infiltration with lymphocytes and plasma cells.

Causal Factors. In adults and in some children the causal factor is undoubtedly the long-continued use of oily nosedrops. However, in some children, especially infants, it is probable that there are other factors, such as some defect in deglutition or in the cough reflex. Lipoid pneumonia is more common in children with cleft palate, and in children with some birth injury. It is also more likely to occur in debilitated children with general weak-

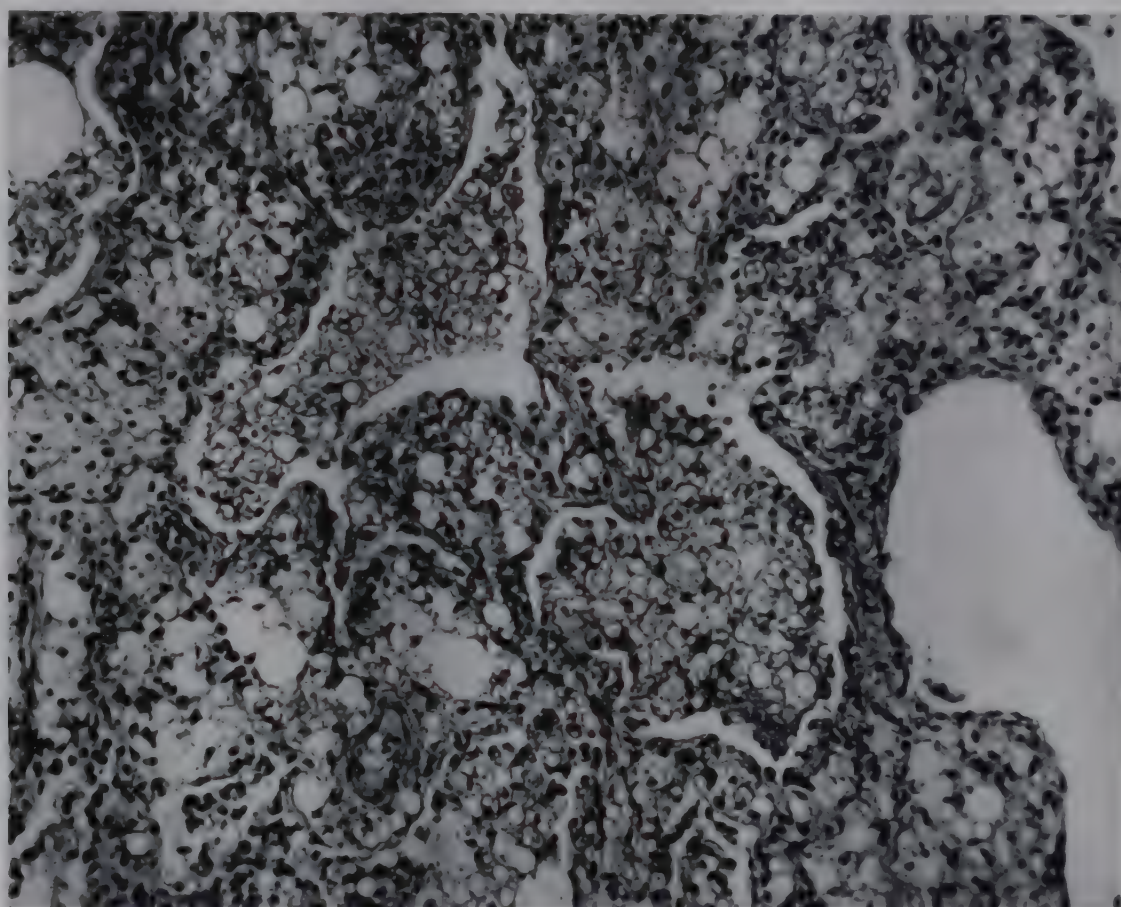


Fig. 267. Lipoid pneumonia.

ness. In some foci the alveolar walls are thickened by fibrous tissue proliferation, and the alveoli are lined by cuboidal cells. The regional lymph nodes contain phagocytic cells filled with vacuoles of fat.

Lipoid Pneumonia Caused by Relatively Bland Oils. In the lower lobes of the lungs there are spherical or pyramidal foci of consolidation in intimate association with the bronchi. These areas are gray and moderately firm, and sometimes contain small yellow foci. Pressure upon the area causes fat to exude. The alveolar walls are irregularly thickened by the proliferation of a moderately collagenous connective tissue. The greater part of the fat is in the form of large droplets, surrounded by an occasional giant cell. There are also a few mononuclear cells with fine vacuoles.

ness of the muscles, and therefore with an inability to cough with sufficient vigor to empty the bronchi (Walsh and Cannon).

The degree of reaction to an oil within the lung probably depends on the free fatty acid content of the oil. Thus chaulmoogra oil, with an acid value of 28, causes acute necrosis of the lung, while iodized sesame oil, which is largely innocuous, has an acid value of 2.5 (Pinkerton). The vegetable oils are in general less irritating than the animal fats. Cod-liver oil, when oxidized, becomes acid-fast, and membranes formed in lipoid pneumonia caused by cod-liver oil can be identified by this means (Graef). It has been shown that saline solutions of drugs commonly employed in the nose do not bring about pathologic changes in the lungs (Walsh and Cannon).

Clinicopathologic Correlation. The clinical symptoms depend upon whether or not an acute pneumonia is associated with the pathologic processes directly resulting from the presence of the oil. In children there are the usual signs of partial consolidation of the lung, and usually a greater degree of cyanosis than would be expected. In adults with lesions caused by mineral oil, there are in most cases no symptoms, and the lesion is discovered as an incidental finding at autopsy.

Ethyl Alcohol

It is customary to consider two types of alcoholism, acute and chronic. It is generally agreed that a concentration of alcohol in the blood above 0.15 per cent deprives a person of full voluntary control (Jetter).

Acute Alcoholism. Occasionally a person is found dead some hours after the ingestion of a large quantity of intoxicating beverages. At autopsy there are found petechiae and mucosal erosions of the stomach; edema, hyperemia, and petechiae of the lungs; hyperemia of the kidneys and liver; and edema and hyperemia of the brain. In many instances there is trauma to some part of the body, and this may be of greater importance as a cause of death than the direct effects of alcohol. A concentration of 0.5 per cent of alcohol in the blood is usually lethal.

Chronic Alcoholism. Chronic alcoholism is difficult to define, but in general it may be said that persons who consume intoxicating beverages in such quantities as to remain under their influence for a greater part of the time fall into this class. Most of these persons have chronic gastritis, occasionally progressing to atrophy of the gastric mucosa, but do not show any higher incidence of gastric ulcer or gastric carcinoma than others. The liver is frequently large and yellow, and most of the liver cells are distended with a single large vacuole of fat. In general there is less arteriosclerosis than in nonalcoholics. It has been assumed that the conspicuous association of lobar pneumonia with chronic alcoholism is caused by the exposure to the elements and inadequate clothing common to persons of this sort. However, some experimental evidence indicates that the phagocytic activity of the polymorphonuclear leukocytes of animals given alcohol is not as great as that of nor-

mal animals. The important individual diseases frequently attributed to alcohol are in reality vitamin deficiencies resulting from the inadequate intake of food (Wright).

Methyl Alcohol. Pathologic changes in acute and chronic poisoning with methyl alcohol are not characteristic except for the degeneration of the ganglion cells in the retina and consequent atrophy of the optic nerves.

Anesthetic Agents

General Anesthetics. In general there are about 1.5 deaths per thousand operations in the operating room. About three-fourths of these are unrelated to the anesthetic. Of the remaining one-fourth, adequate explanation of death such as edema of the larynx or aspiration of vomitus is found at autopsy in one-half, while in the other half there are no anatomic changes in the tissue. There is no significant difference in the mortality with the various anesthetic agents (Lyford, Berger, and Shumacker).

Delayed Chloroform Poisoning. Following the inhalation of chloroform for a relatively long period of time there are central necrosis of the liver and rarely acute yellow atrophy. A high content of protein and glycogen in the hepatic cells minimizes the toxic effect of chloroform.

Barbiturates. There is an increased sensitivity to the barbiturates in persons with hepatic damage and in alcoholics (Jetter and McLean). Anatomic changes are nonspecific, and include edema and hyperemia of the lungs, liver, kidneys, and brain. In delayed death there is usually bronchopneumonia, and occasionally there are degenerative changes in the renal epithelium.

The most satisfactory method for establishing barbiturate poisoning is to isolate the pure drug from tissue or fluids. In fatal cases the average recovery is 3.5 mg. per 100 gm. of tissue.

Local Anesthetics. Rarely a person collapses, and more rarely dies, following the application of local anesthetics to the mucous membranes of the body, either by injection or on the surface. The pathologic findings at autopsy consist essentially of congestion of the viscera. Of forty-three deaths studied by a committee of the American Medical Association, twenty-six followed the use of cocaine (Mayer).

Cyanide

Cyanide, in the form of hydrocyanic acid, is a protoplasmic poison for all members of the animal kingdom from protozoa to man. The lethal dose in man is about 50 mg.

Pathologic Anatomy. There are petechiae in the skin, and cyanosis of the face, neck, and extremities. At autopsy, the odor of hydrogen cyanide is almost invariably noticeable. The blood is generally dark and remains fluid for many hours following death. The mucous membranes of the lip, mouth, and esophagus may be swollen and discolored, but cor-

ing an agent which will bind or destroy the cyanide and spare the enzymes (Hanzlik and Richardson).

Sulfonamide Compounds

The frequent use of the sulfonamide compounds by both the medical profession and the laity has focused attention not only on the remarkable effectiveness but also on the deleterious action of the group.

Incidence of Reaction. It is not possible to collect complete data, but it is estimated that there is not more than one death from the

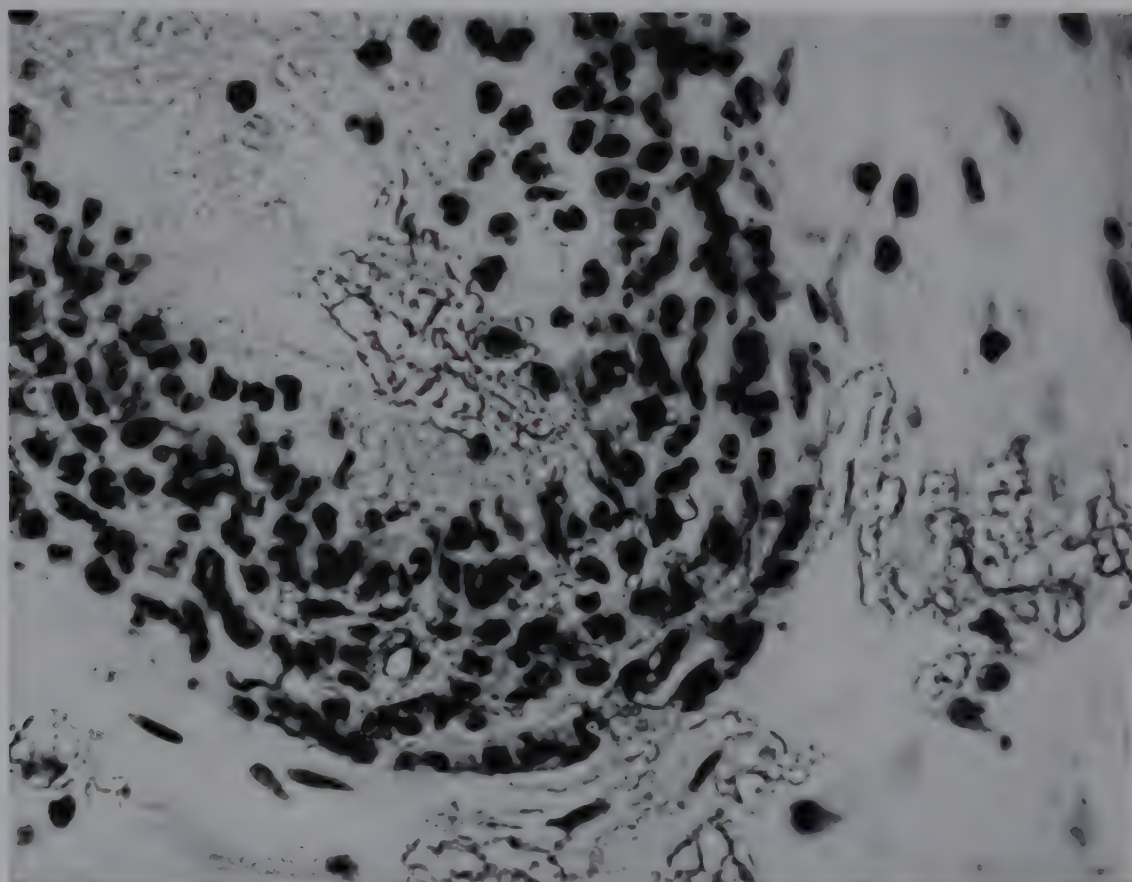


Fig. 268. Acute arteritis in a cerebral vessel adjacent to microcrystals of sulfathiazole introduced intrathecally. The basic disease was tuberculous meningitis.

rosion is rare. The mucous membrane of the stomach is swollen and shows many petechiae. In the serous membranes there are usually petechiae. If the patient survives for any length of time, there is fatty degeneration of the liver, and bloody urine is found in the bladder. There are edema, hyperemia, and hemorrhage in the organs noted, and in the brain. In chronic poisoning the brain shows the principal pathologic change: degeneration of the ganglion cells and slight lymphocytic infiltration about the vessels (Gettler and St. George).

The mechanism of action of cyanide is described as interference with the oxidative enzymes. Treatment must depend upon furnish-

sulfonamides for each 1610 cases of pneumonia in a community (Sutliff, Helpert, Griffin, and Brown). The incidence of nonfatal reactions of some sort varies with the specific drug from 3 or 4 per cent to over 70 per cent.

Types of Reaction. The sulfonamide compounds may affect tissue either mechanically or clinically.

Mechanical Effects. Crystals of the drug deposited in the tissue or in serous cavities incite a foreign body reaction and adhesions. Excessive concentration in the urine will result in precipitation of crystalline or amorphous material in the urinary tract, which if in sufficient amount may occlude the ureter and cause uremia.

Chemical Effects. The sulfonamide in solution in the body fluid probably produces pathologic change in two ways: by direct toxic effect on certain tissues and cells, and in combination with a protein by establishing sensitization. It is difficult to separate the two actions. Throughout many viscera there is infiltration with eosinophils, most marked in the myocardium (French and Weller). Foci of necrosis may be seen in the lungs, liver, spleen, kidneys, adrenals, lymph nodes, and bone marrow. In hemolytic anemia there is erythroblastic hyperplasia of the marrow, and discontinuance of the drug is usually followed by recovery. The lesions in the kidney, probably a direct toxic effect, are cloudy swelling, fatty degeneration, and necrosis of the epithelium. Anatomic change in the brain results from endothelial injury with thrombosis and hemorrhage. Histologic studies of the rash reveal a nonspecific type of inflammation (Simon). The hypersensitive type of reaction usually takes the form of polyarteritis or of a severe interstitial nephritis.

Alkaloids

The pathologic changes in fatal poisoning with alkaloids are not characteristic. There are usually hyperemia, edema, and hemorrhage in the gastro-intestinal tract, lungs, and brain. With nicotine, the odor of tobacco may be apparent. After strychnine, rigor mortis may set in rapidly and persist for many hours or days. In chronic ergot poisoning some persons develop a symmetrical gangrene of the extremities. In any suspected addict, search should always be made for the scars of needle punctures and the indolent subcutaneous abscesses so characteristic of the drug addict.

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LXVII

Diseases Caused by Inorganic Substances

Inorganic poisons may be introduced into the body accidentally, with suicidal intent, or during the use of the substance as a therapeutic agent. The more important of the inorganic poisons are the mineral acids and alkalis, phosphorus, and the metals, mercury, lead, arsenic, gold, bismuth, and silver.

Corrosive Acids and Alkalis

The strong acids and alkalis act on tissue by extracting water, by coagulating or combining with protein, and by forming acid or alkaline hematin from hemoglobin.

Pathologic Anatomy. The mucous membranes of the mouth, esophagus, and stomach become dry and black when sulfuric acid or hydrochloric acid is taken in concentrated solution, and yellowish green after nitric acid. After strong alkalis the mucosa is first edematous and bright red, and later brown or black. With more dilute acids and alkalis the necrotizing action is more severe on the crests of the gastric rugae. If recovery takes place, there is likely to be cicatricial contraction of the esophagus and stenosis of this hollow viscus.

The most common source of poisoning with ammonia is a break in the lines of a refrigerator. Within a few hours there is congestion and edema of the mucous membrane of the pharynx and larynx. The conjunctivas are hyperemic, the eyelids edematous, and the lacrimal glands hyperactive. Congestion of the lung and focal areas of bronchopneumonia (Caplin) occur in the severe cases.

Phosphorus

The poisonous effects of yellow phosphorus may be: (1) a burn of the skin from contact, (2) fulminating poisoning from inhalation of vapors, and (3) acute poisoning from ingestion.

Pathologic Anatomy. If death occurs within a few hours, there are few pathologic changes except congestion. After one or more days there is profound fatty degeneration of all the viscera, liver, kidneys, heart, and brain (Rubitsky and Myerson). In the liver there is also necrosis, at first peripheral but later involving all zones. The nerve cells of the brain normally containing some lipid become distended with fat (Wertham). The body fluids may be phosphorescent. The burns of the skin are deep and heal slowly.

Sources. Aside from the instances of the deliberate suicidal ingestion of phosphorus, most examples are accidental and follow the ingestion of lucifer matches, fireworks, and rat poison by children (Blumenthal and Lesser). The fatal dose may be as little as 0.097 gm. (1½ grains).

Clinicopathologic Correlation. The pathologic changes in the liver cause enlargement, and after a few days jaundice. There are all of the blood chemical changes of hypofunction of the liver, and the excretion of amino acids in the urine. After recovery, a transverse band of dense bone may appear in the subepiphyseal regions of growing bones.

Talcum Powder

When talcum powder is accidentally dusted into a wound, as from the powder on rubber gloves, the insoluble crystals become embedded in the tissue or deposited on the surface of the peritoneum. There is a foreign body type of reaction, with the formation of small nodules of fibrosis and giant cells. Examination with polarized light reveals the presence of many crystals within the giant cells. Palpable masses of firm tissue have developed within wounds or on the surface of the peritoneum from five to ten years after

laparotomy (Fig. 60, p. 101) (Byron and Welch; Fienberg; Seelig, Verda, and Kidd).

Tattoos

Immediately after tattooing of the skin, there is an acute inflammation of the dermis, and the area is covered by a serosanguineous exudate. After one to three weeks the epithelium regenerates over the punctures, and the exudate is absorbed. The pigment granules are deposited both extracellularly and intracellularly in the dermis. The granules gradually dissolve or are carried to the regional nodes, so that absence of a tattoo mark known to have been present years before does not preclude identification of a body. The mercuric sulfide is the most irritating pigment and occasionally induces a keloid (Rukstinat).

Mercury

The metal, mercury, is not poisonous, but in the form of soluble mercuric salts it is highly toxic. Most examples of poisoning fall into one or two types: acute poisoning from suicidal or accidental ingestion or absorption, and subacute poisoning in those who use a mercuric salt as a therapeutic agent and in workers exposed in industrial plants.

Acute Poisoning. Pathologic changes in mercury poisoning are the result of (1) the direct action on the tissues at the portal of entry, and (2) indirect action on tissue at the point of excretion.

The mucosa of the esophagus and stomach is edematous, dark reddish gray, and opaque, as the result of the coagulation of the superficial layers. After a few days it becomes yellow-green from pigmentation with bile, and may ulcerate. The kidneys are the seat of acute nephrosis. The epithelium of the proximal tubule is necrotic, and after a few days shows extensive calcification (Fig. 14, p. 24) (Edwards). Survival depends largely on the regeneration of the epithelium, which begins on the sixth to the ninth day. In the colon there is an acute necrotizing ulcerative colitis.

Nausea and vomiting are related to the lesion in the stomach, bloody diarrhea and tenesmus to the lesion in the colon, and oliguria, albuminuria, and uremia to the lesion in the kidney. Death occurs on the sixth to the tenth day. A fatal dose is 0.194 to 0.324 gm. (3 to 5 grains).

The same lesions, except for those in the stomach, follow the intravenous injection of mercuric chloride and of mercurochrome (St. George).

Subacute Poisoning. Slow absorption of mercury over long periods leads to many clinical signs and symptoms: stomatitis with inflammation, pigmentation, and ulceration of the gums and buccal mucosa, necrosis of the mandible, peripheral neuritis caused by degeneration of myelin, and obscure abdominal and cerebral symptoms not well correlated with anatomic change.

Lead

Lead poisoning may be acute or chronic, depending on the dose, the rate of absorption, and the degree of storage in the tissues.

Acute Poisoning. Acute poisoning is rare except after the ingestion, usually accidental, of a soluble lead salt. Mild acute gastritis and enteritis occur, as well as degenerative changes in the kidneys.

Chronic Poisoning. Plumbism. The outstanding changes of plumbism are in the red cells, in the gums, in the smooth muscle, in the peripheral nerves, and in the brain.

The rate of destruction of red cells is accelerated, presumably by an increased lability from a deposit of lead sulfide on the surface of the cells. The bone marrow is hyperplastic. Stippled cells are probably degenerating reticulocytes. The lead line on the gums is a perivascular deposit of lead sulfide in the submucosal papillae. The effect on smooth muscle is physiologic, causing spasm and hence the clinical symptom of colic. The peripheral nerves, especially those to the extensor muscles of the wrist, show degeneration of myelin, and after many months or years degeneration of the axis cylinders and of the cell bodies in the spinal cord. The denervated muscles are atrophic. Lead encephalopathy is more common in children and consists of mild or severe edema of the brain and proliferation of endothelial cells leading to ischemic loss of nerve cells and gliosis (Akelaitis).

Poisoning with Tetra-ethyl Lead. The inhalation of the fumes of ethyl gasoline may lead to intoxication, at times fatal. The pathologic changes are intense congestion and hemorrhage in the lungs, congestion of the viscera

and brain, and agglutinative thrombi in the cerebral capillaries. A volatile lead compound can be isolated from the brain (Norris and Gettler).

Sources. Today most lead poisoning is industrial—in painters, lead-smelters, and storage-battery workers. The material is stored in the bones, and the effect is cumulative.

Arsenic

In general, arsenic may be looked upon as a vascular poisoning, producing degenerative lesions in small blood vessels.

Arsenical Dermatitis. Dermatitis occurs

Acute Poisoning by Ingestion. Large doses of arsenic by mouth produce an acute inflammation of the stomach and intestine, fatty degeneration of the viscera, necrosis of the liver, and multiple petechiae and ecchymoses in many tissues.

Sources. In addition to the types related to the therapeutic use of arsenic, and homicidal and suicidal poisoning, many accidental poisonings are seen: from ingestion of fruits and vegetables sprayed with arsenic compounds, and from inhalation of arsenic generated in industrial plants or by the action of molds on wallpaper.

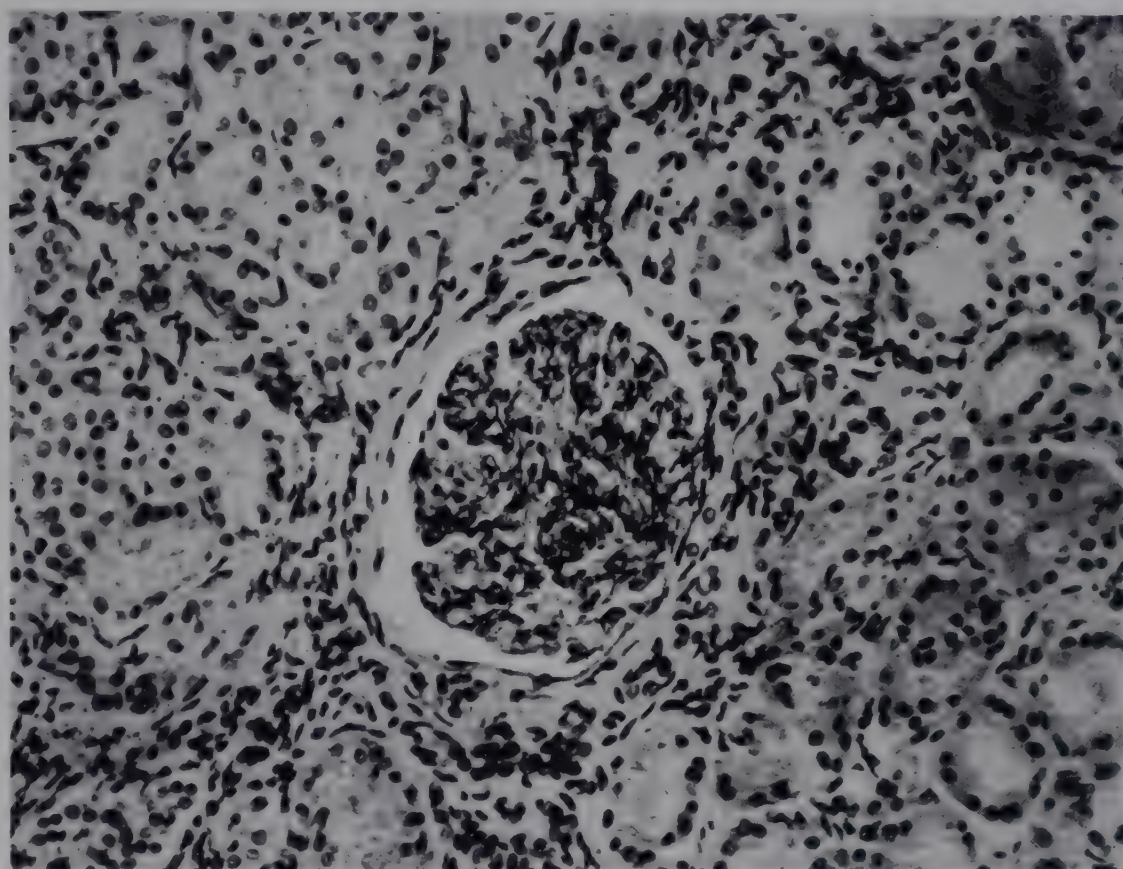


Fig. 269. Kidney in argyria, showing a fine deposit of silver in the endothelial cells of a glomerulus.

most frequently with quintivalent arsenic, and the element may be demonstrated in the ectodermal structures by histochemical methods. Trivalent compounds localize in the dermal arterioles and capillaries (Osborne). In chronic dermatitis, pigmentation and palmar and plantar keratoses are observed. Transformation to an epidermoid carcinoma is not uncommon (Montgomery and Waisman).

Arsenical Encephalopathy. Occasionally in chronic poisoning, but more commonly following the use of arsphenamine, there is mild encephalitis (Ecker and Kernohan) or multiple foci of hemorrhage in the brain (Globus and Ginsburg). Further discussion of the reactions to arsphenamine is given in Chapter XLII, p. 340.

Gold

Gold in the form of complex salts is used in the treatment of many diseases, notably pulmonary tuberculosis, lupus erythematosus, and rheumatoid arthritis (Driver and Weller). Reactions, both immediate and delayed, are observed, and in a few instances death results. The most consistent pathologic findings are cloudy swelling and necrosis of the renal epithelium, central necrosis of the liver, and ulcerative enteritis and colitis (Anderson and Palmer).

Chrysiasis. This is a permanent pigmentation of the skin caused by the parenteral use of gold preparations, and subsequent exposure of the skin to ultraviolet radiation. The

color of the skin varies from a light gray to a bluish violet or a brownish yellow. Microscopic examination reveals small black granules of pigment in the endothelial and adventitial cells of the capillaries of the dermis (Schmidt).

Silver

After two to three years of continuous absorption of silver salts, a peculiar pigmentation of the skin appears, known as "argyria." The bluish gray color of the skin is slightly more prominent in the folds of the skin and on those parts exposed to sunlight. Death rarely results directly from argyria.

In the skin there are small black granules in the membrana propria of the sweat glands and in the connective tissue about the sebaceous glands and hair follicles. There is no inflammation, and no deposit of the granules of silver in epithelium (Hill and Montgomery).

In the viscera similar black granules are found in moderate numbers in the endothelium of the liver, spleen, and kidney. On occasion the deposit within the endothelium of the glomeruli may be abundant, and may result in proliferation of fibrous tissue and contraction of the kidney.

Bismuth

If bismuth salts are given in small doses over a long period of time, there is pigmentation of the skin similar to that in argyria. At autopsy, pigmentation may also be found in the colon and in other mucous membranes (Lueth, Sutton, McMullen, and Muehlberger).

If larger doses are given over a shorter period of time, acute poisoning may supervene. There are a necrotizing colitis, necrosis of the renal epithelium, and cloudy swelling and necrosis of the liver, similar to the changes in poisoning with mercury (Mayer and Baehr).

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PART V

DISEASES CAUSED BY DEFICIENCIES

LXVIII

Diseases Caused by a Deficiency of Vitamins

For the proper growth and metabolism of the animal organism a large variety of substances is required. Protein, fat, carbohydrate, minerals, and water, taken in through the gastrointestinal tract, are broken down there and rebuilt into specific animal protoplasm. Some other necessary substances are manufactured in the body by specific organs or tissues, and are designated as hormones. Others cannot be synthesized by the animal and must therefore be furnished from an outside source. These are known as the "accessory food factors" or the "vitamins."

A Broad Concept of Deficiency Diseases

The original investigators thought of a deficiency of a vitamin as a decreased amount of or an absence of a substance in the diet. This concept has been gradually broadened until at the present time at least six types of deficiency must be recognized: inadequate intake, inadequate digestion, inadequate absorption, increased requirement, inadequate utilization, and loss by excretion (Mackie, Eddy, and Mills).

1. **Inadequate Intake.** In this category there are at least three types: an inadequate diet because of economic position or dietary habits, inadequate diet because of disease leading to anorexia or vomiting, and the use of artificial diets for medical or nonmedical reasons. The patient placed on a reducing diet, the patient with a peptic ulcer or some other disease of the gastro-intestinal tract who requires a special diet, and the pregnant woman must all be given adequate amounts of vitamins.

2. **Inadequate Digestion.** In the child with pancreatic fibrosis or in the adult with pancreatic calculi and obstruction of the duct

there is steatorrhea as the result of the absence of pancreatic enzymes and the lack of digestion of fats. This eventually leads to emaciation. At the same time there is inadequate absorption of the fat-soluble vitamins. In the patient with Addisonian pernicious anemia the primary difficulty appears to be the absence of the intrinsic factor in the gastric juice. This is associated with atrophy of the gastric mucosa.

3. **Inadequate Absorption.** To be of use to the animal organism the vitamins must not only be present in the diet in adequate amounts, but they must be absorbed into the blood stream. Simple disturbances, such as long-continued vomiting or diarrhea, may prevent the substance from being present in the intestine long enough to be absorbed (Dann and Cowgill). Similarly a gastrocolic fistula short-circuits the food so that little of it is exposed to the mucosa of the small intestine (Urmy, Rogle, Allen, and Jones). Other substances in the intestine, such as mineral oil, will hold the fat-soluble vitamins in the intestine. Destruction of the mucosa of the intestine by chronic ulcerative or fibrotic processes or surgical removal of a length of the intestine may interfere with the absorption of vitamins. The absence of bile may prevent the absorption of the fat-soluble vitamins (Lord, Andrus, and Moore). Many of these conditions make it necessary to administer the vitamins parenterally in order to maintain the normal metabolism.

4. **Increased Requirement.** Many of the vitamins are actually parts of essential enzyme systems concerned in metabolism. When the rate of metabolism is increased, as it is in hyperthyroidism (Wohl and Feldman), in the fever of infectious diseases (Getz, Hildebrand, and Finn), during exercise, and during pregnancy and lactation (Ricketts), the re-

quirement for one or all of the vitamins may be materially increased. For example, active pellagra may appear suddenly after the onset of an infectious disease or during the increased metabolism following the administration of glucose and insulin to diabetic patients (Sydenstricker, Geeslin, and Weaver).

5. Inadequate Utilization. Many of the vitamins undergo revision within the body or enter into some chemical reaction. If the organ in which these processes occur is the seat of disease, the result will be a deficiency of that vitamin, regardless of the amount within

Toxic Effects of the Vitamins

All vitamins are toxic if a large dose is given. Fortunately the ratio between daily requirement and toxic dose is large: for example 1:600 for 2-methyl-1, 4 naphthoquinone (vitamin K), 1:2000 for vitamin D, 1:7500 for vitamin A, 1:25,000 for thiamine, and 1:60,000 for pyridoxine.

Avitaminosis A

Pathologic Anatomy. In the usual clinical case of vitamin A deficiency there is moderate

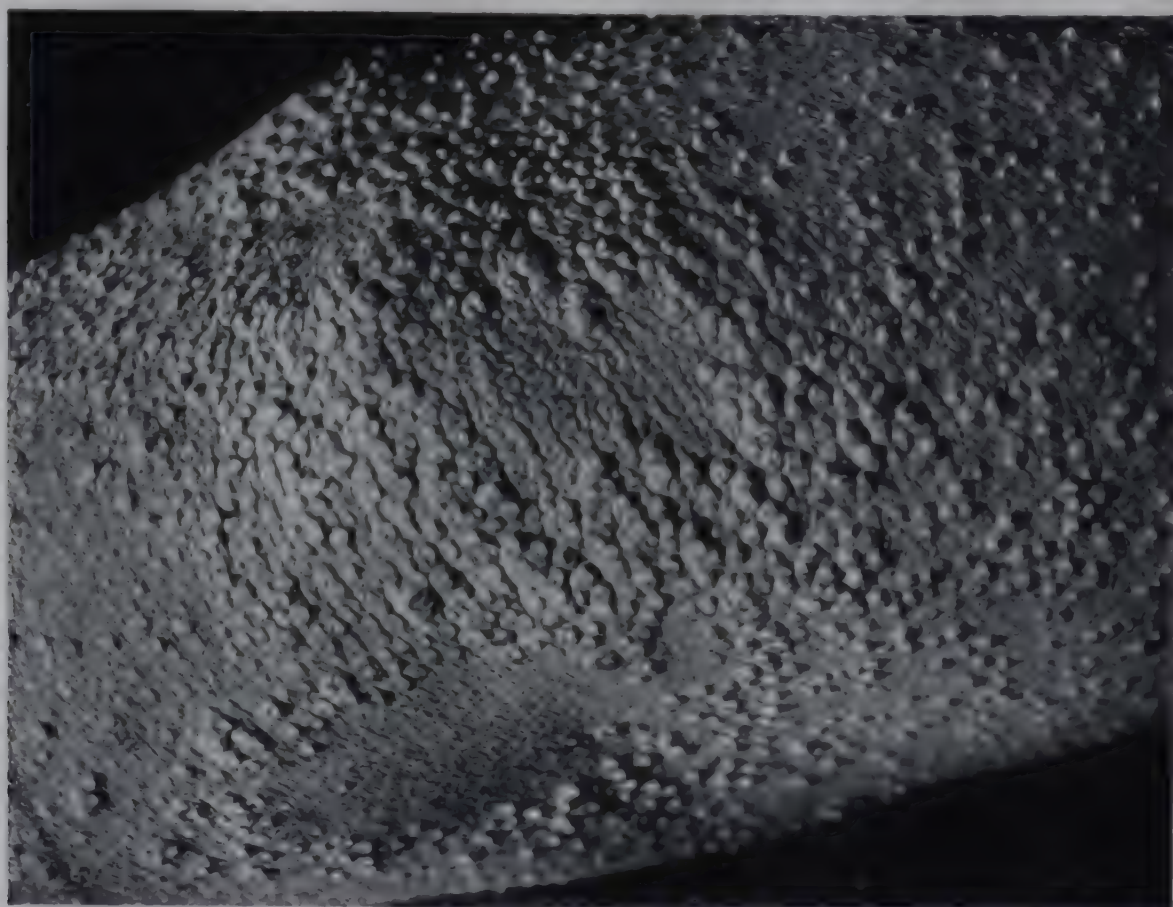


Fig. 270. Focal hyperkeratosis of the skin in vitamin A deficiency. (Photograph by courtesy of Prof. C. H. Hu.)

the diet. For example, there is decreased conversion of carotene into vitamin A by the liver in cirrhosis (Patek and Haig), and in diabetes in children (Brazer and Curtis). In many diseases of the liver there is a decreased plasma prothrombin and consequent inability of the patient to respond to either orally or parenterally administered vitamin K.

6. Loss by Excretion. The water-soluble vitamins are contained in almost constant amounts in the urine and in the perspiration. Excessive sweating has been known to cause scurvy (Bernstein), and excessive loss of water in the urine, as in diabetes insipidus, has resulted in pellagra (Vogt-Moller).

or severe emaciation. The skin, mucous membranes, and organs are pale in color as the result of an associated anemia. The subcutaneous deposits of fat are inconspicuous, and the musculature is atrophic. However these findings are common to most of the vitamin deficiencies and to undernutrition in general, and may not result from the deficiency of vitamin A. The same is true of the atrophy of the spleen and lymph nodes and the hemosiderosis of the spleen, and at times of the liver. There is, however, in experimental animals, evidence that these latter changes disappear on the administration of the specific vitamin, indicating a cause-and-effect relation.

The specific changes resulting from a deficiency of vitamin A affect the epithelial structures throughout the entire body. These are most manifest externally in the eye and skin. The cornea shows areas of dryness, thickening of the epithelium, loss of luster, and wrinkling of the surface. Later the cornea is softened with ulceration and secondary invasion by bacteria—keratomalacia (Fig. 271). In the skin there are numerous small, elevated, horny papules, varying from 1 to 2 mm. in diameter (Frazier and Hu), seen more frequently in adults than in children. In the teeth, in man, it is difficult to delineate accurately the pathologic lesions caused by vitamin deficiency. It

ureters, salivary glands, uterus, and periurethral glands. The basal layer of the epithelium is preserved and the normal glandular of transitional epithelium is replaced by a thick layer of squamous cells. The surface is a mass of keratinized epithelium, and the lumens of the smaller structures may be filled with a keratinized mass. Within the keratinized material there is evidence of acute inflammation, as shown by the migration of polymorphonuclear leukocytes and fluid.

In growing bones there is histologic evidence of a cessation or decrease in the rate of bone growth. The cartilage is atrophic and the trabeculae of the primary spongiosa are



Fig. 271. Keratomalacia. (Armed Forces Institute of Pathology, Neg. No. 69434.)

is supposed by many that the hyperplasia of the enamel, with ridge formation, is related to this condition, but this supposition has not been proved (Mellanby). In the lungs there are usually an associated bronchitis and bronchopneumonia with abscess formation, and at times a definite bronchiectasis. The pancreas is small and firm, and frequently contains numerous small cystic spaces. The remaining organs show no essential gross pathologic change.

The specific microscopic effect of the deficiency of vitamin A is a squamous metaplasia of the epithelium, found most frequently in the trachea and bronchi and in the pelvis of the kidney. It is also found in the conjunctiva, in the periocular glands, in the mucosa of the nares, in the accessory sinuses, pancreas,

narrow and poorly formed. At the junction of cartilage and bone there is a parallel-plate of calcified osteoid tissue.

Clinicopathologic Correlation. From the clinical standpoint, the most important effects of vitamin A deficiency are the general emaciation, the anemia, the delayed growth of bone, and the greater incidence of infection. So far as can be determined by careful histologic and experimental studies, the greater incidence of infection is the result of a break in the surface continuity of epithelial structures and secondary invasion by bacteria which are already growing in large numbers in the accumulated keratinized material. The administration of vitamin A has no effect on an infection which is already established. In the respiratory tract there are in addition inade-

quate moistening of the surface, and inadequate emptying of the bronchial tree because of the replacement of the ciliated mucus-secreting epithelium by a keratinized epithelium. In smaller hollow viscera the accumulation of keratinized material may cause obstruction, another predisposing factor in infection. The obstruction of the pancreatic ducts by this mechanism may play a role in the emaciation and loss of weight. In animals the keratinization of the epithelium in the urinary tract is associated with the formation

Avitaminosis B: Beriberi and Polyneuritis; Wernicke's Disease; Pellagra; Ariboflavinosis

When vitamin B was first discovered as an antineuritic vitamin, valuable in the treatment of beriberi, it was thought to be a single entity. In 1926 a sharp separation into a thermostable and a thermolabile fraction was demonstrated. These two basic types remain the best basis for classification of the components of vitamin B. By various other means they



Fig. 272. Vitamin A in liver as shown by photography with ultraviolet rays. (Photograph by courtesy of Dr. Hans Popper.)

of calculi (Higgins). There is no direct evidence that the same is true in man (Jewett, Sloan, and Strong). The decrease of visual purple in the eye is responsible for hemeralopia, or night blindness, and this clinical phenomenon serves as one of the most satisfactory tests for vitamin A deficiency. As vitamin A is a fat-soluble substance, the absence of bile from the gastro-intestinal tract, as in obstructive jaundice, may induce or exaggerate the deficiency state (Altschule). In northern India the lathyrus pea, which when eaten causes lathyrism, may contain a toxic substance which interferes with the proper utilization of vitamin A (Mellanby).

have been further subdivided until today at least twenty-one substances are recognized. Some of these are indefinite, such as vitamin B₅, and still others, with further advances in chemical isolation and identification, will be found to be identical with other factors (Elvehjen).

Thiamine. *Beriberi and Polyneuritis.* PATHOLOGIC ANATOMY. Beriberi is characterized by multiple peripheral neuritis, myocardial failure, generalized edema, and muscular atrophy, and is caused by a deficiency of vitamin B₁ or thiamine. It is endemic in the Orient and is occasionally seen in the Occident (Weiss and Wilkins).

The most constant and important anatomic lesions of beriberi are in the heart, peripheral nerves, subcutaneous tissues, and serous cavities. The heart is dilated and is occasionally hypertrophic. The dilatation is more conspicuous on the right side than the left and in the atria than in the ventricles. The conus arteriosus of the right ventricle is especially affected. The myocardium of the affected chambers may show degenerative changes such as cloudy swelling, hydropic degeneration, and fatty degeneration. The interstitial tissue is edema-

with beriberi—the so-called “wet” type—there is widespread edema of the subcutaneous tissue and of the serous cavities. There may be an associated chronic passive congestion of the viscera.

It is apparent that the anatomic diagnosis of beriberi is one of both inclusion and exclusion—inclusion in that dilatation of the heart, degeneration of the peripheral nerves, and anasarca are demonstrable, and exclusion in that there are no other lesions to account for the signs and symptoms or for death.



Fig. 273. Degeneration of myelin in a peripheral nerve in athiaminosis. From a patient with carcinoma of the stomach. (Slide by courtesy of Dr. Harry Zimmerman.)

tous, and there is slight infiltration with lymphocytes. The peripheral nerves are grossly normal, but microscopically show degeneration of myelin. In advanced cases there are fragmentation of the axis cylinders and wallerian degeneration. Similar lesions of the cranial nerves and of the sympathetic nerves have been observed. The muscles supplied by the affected nerves are atrophic. Changes in the central nervous system are inconspicuous and are limited to slight demyelination in the posterior columns and chromatolysis in the motor ganglion cells. The reported hypertrophy of the islands of Langerhans, medulla of the adrenal, thyroid, and hypophysis has not been sufficiently studied. In some patients

CLINICOPATHOLOGIC CORRELATION. Beriberi occurs in acute and chronic forms and in so-called “wet” and “dry” forms. The edema of the “wet” form is most readily explained on the basis of cardiac failure, but it is noteworthy that edema occurs predominantly in those with a general dietary deficiency, hence it is probable that hypoproteinemia also plays a role. The changes in the heart are directly responsible for the signs and symptoms of cardiac failure: dyspnea, cyanosis, and low blood pressure. These symptoms may appear suddenly, especially in children, and may progress rapidly to death (Wenckebach). The effect on the heart of a deficiency of thiamine is probably an inter-

ference with the utilization of carbohydrate, but the reason for selective action on some chambers is not understood. Although no precise clinicopathologic studies in the early stages of the disease have been made, it is assumed that degeneration of the nerves accounts for the loss of strength, easy fatigability, soreness of the muscles, neuritic pains, paresthesia, and anesthesia. Involvement of the nerves begins peripherally and is usually more marked in the legs than in the arms.

In early stages administration of thiamine is followed by spectacular recovery within a matter of hours, but in chronic deficiency, many weeks or months may be required to complete the repair of the lesions and restore normal function.

ISOLATED POLYNEURITIS. In the Occident a polyneuritis caused by a deficiency of thiamine is observed in patients who do not show the other changes of beriberi (Fig. 273). The related and probably causal conditions are chronic alcoholism (concomitant deficient diet), pregnancy (increased demand), cachexia and emaciation (inadequate diet), and diabetes (unknown). The pathologic changes in all are identical with those of beriberi.

Wernicke's Disease. **PATHOLOGIC ANATOMY.** In the classical case of Wernicke's disease there are lesions in the paramedian and the paraventricular nuclei of the thalamus and hypothalamus, the mammillary bodies, the para-aqueductal region of the midbrain (nuclei of the third and fourth nerves), the nucleus of the sixth nerve, the triangular nucleus and the nucleus of Bechterew of the vestibular nerve, and the dorsal nucleus of the vagus nerve. These lesions are characterized by degeneration of ganglion cells and hemorrhage into the surrounding tissue. The smaller blood vessels in the region are dilated and tortuous. There is a slight reaction of the glia with formation of numerous gitter cells, but there is no infiltration with lymphocytes or leukocytes. Occasionally lesions are found in the spinal cord, especially in the dorsal gray matter of Clarke's column. The original designation, "superior hemorrhagic polioencephalitis," is an undesirable name, since the basic lesion is not an inflammation.

Following the original description of the disease by Wernicke many examples of the disease were observed in chronic alcoholics, and it became accepted that this lesion was

caused by some toxic effect of alcohol. Experimental investigations, however, leave no doubt that the condition is the result of a deficiency of thiamine. In most of the patients there are other evidences of vitamin deficiency such as peripheral neuritis, scurvy, and cheilitis. Occasionally there is outspoken pellagra. In pigeons and in some mammals an exactly identical pathologic lesion results when the diets are deficient in thiamine, but contain an excessive amount of the other vitamins.

CLINICOPATHOLOGIC CORRELATION. The clinical symptoms are variable and depend on the exact location of the pathologic lesions. The involvement of the nuclei supplying the ocular muscles leads to ophthalmoplegia. The consistent clouding of consciousness may be caused by a lack of thiamine, but it is probably related in addition to other deficiencies, as lack of carbohydrate, oxygen, niacin, or riboflavin. The ataxia is difficult to explain, but it is possible that the brachium conjunctivum becomes involved because of contiguity (Jolliffe, Wortis, and Fein).

Niacin. Pellagra. The name pellagra is derived from the Italian words "pelle agra," meaning rough skin. The disease was first recognized in Spain in 1735 under the title "mal de la rosa." Endemic and sporadic cases were seen in the United States throughout the nineteenth century, but it was not until 1907 that the widespread prevalence of pellagra in the southern United States was pointed out by Searcy.

The conquest of pellagra began with the experiments of Chittenden and Underhill, who produced a condition known as "black tongue" in dogs by feeding an artificial diet. Subsequently many investigators, among them Goldberger, noted the similarity of canine black tongue to human pellagra. Finally Elvehjem and his associates effected the cure of canine black tongue with nicotinic acid, and suggested that the same substance might be the key to the cure of pellagra. The first reports of the treatment of pellagra with nicotinic acid were most encouraging. Within one to three days the fiery redness of the oral, pharyngeal, and vaginal mucous membranes disappeared. The associated Vincent's infection healed rapidly. Nausea, vomiting, and excessive salivation decreased, and the bowel movements became normal. The appetite in most cases returned, and abdominal pain and

discomfort disappeared. The acute mental symptoms were usually quickly alleviated, and the patient became calm and mentally clear. Truly medicine had worked a miracle. Patients who had been in mental asylums for several years were restored to a reasonably normal social existence. But many symptoms and signs remained. The patients were not restored to complete physical well-being by this one chemical substance. Now more clearly shown were the cheilitis and corneal vascularization resulting from ariboflavinosis, the

are some fallacies in this reasoning, but it is the most plausible approach at the present time.

PATHOLOGIC ANATOMY. The skin in the early stages of pellagra shows a slight erythema, which progressively increases until the skin appears as a fiery red, thick, edematous tissue (Fig. 274). In the less severe cases, or during the process of healing, there is desquamation and a brown pigmentation. There is little microscopic change in the basal layer. There are acanthosis and slight parakeratosis.



Fig. 274. Hyperpigmentation of the dorsum of the hands in pellagra. (Photograph by courtesy of Dr. Tom Spies.)

weakness and pain resulting from a deficiency of thiamine, the macrocytic anemia resulting from a lack of the extrinsic factor, and many other poorly understood lesions and complaints (Spies, Bean, and Ashe).
From these findings it is clear that human pellagra is not a disease caused by a deficiency of a single vitamin, but rather results from the lack of a combination of accessory food factors, possibly all of the B complex. The pathologic effects of a deficiency of thiamine, niacin, riboflavin, pyridoxine, and pantothenic acid will be discussed separately. In these discussions it is assumed that if one of these specific substances has a therapeutic effect on a specific lesion in pellagrins, that lesion results from a deficiency of this substance. There

The superficial layer of keratinized cells is greatly increased in thickness and there are small granules of the brown pigment throughout this layer. In the dermis there is edema, both between the cells and in the individual collagen fibers. The blood vessels are dilated and the intercapillary pegs are conspicuous. There is a slight infiltration of lymphocytes, especially about the blood vessels. During healing or in the chronic cases there is atrophy of the epidermis, with obliteration of the rete pegs (Fig. 275). In the areas of skin not clinically involved, there are similar but less severe changes (Moore, Spies, and Cooper).
Inside the mouth the changes in the tissues of the tongue and of the cheek are similar to those in the skin. Throughout the gastro-

intestinal tract there is inflammation of a degree comparable with that in the skin, but modified by the histologic structure of the mu-

cells without inflammatory reaction. In acute cases edema and congestion are conspicuous. In general there are no pathologic changes in

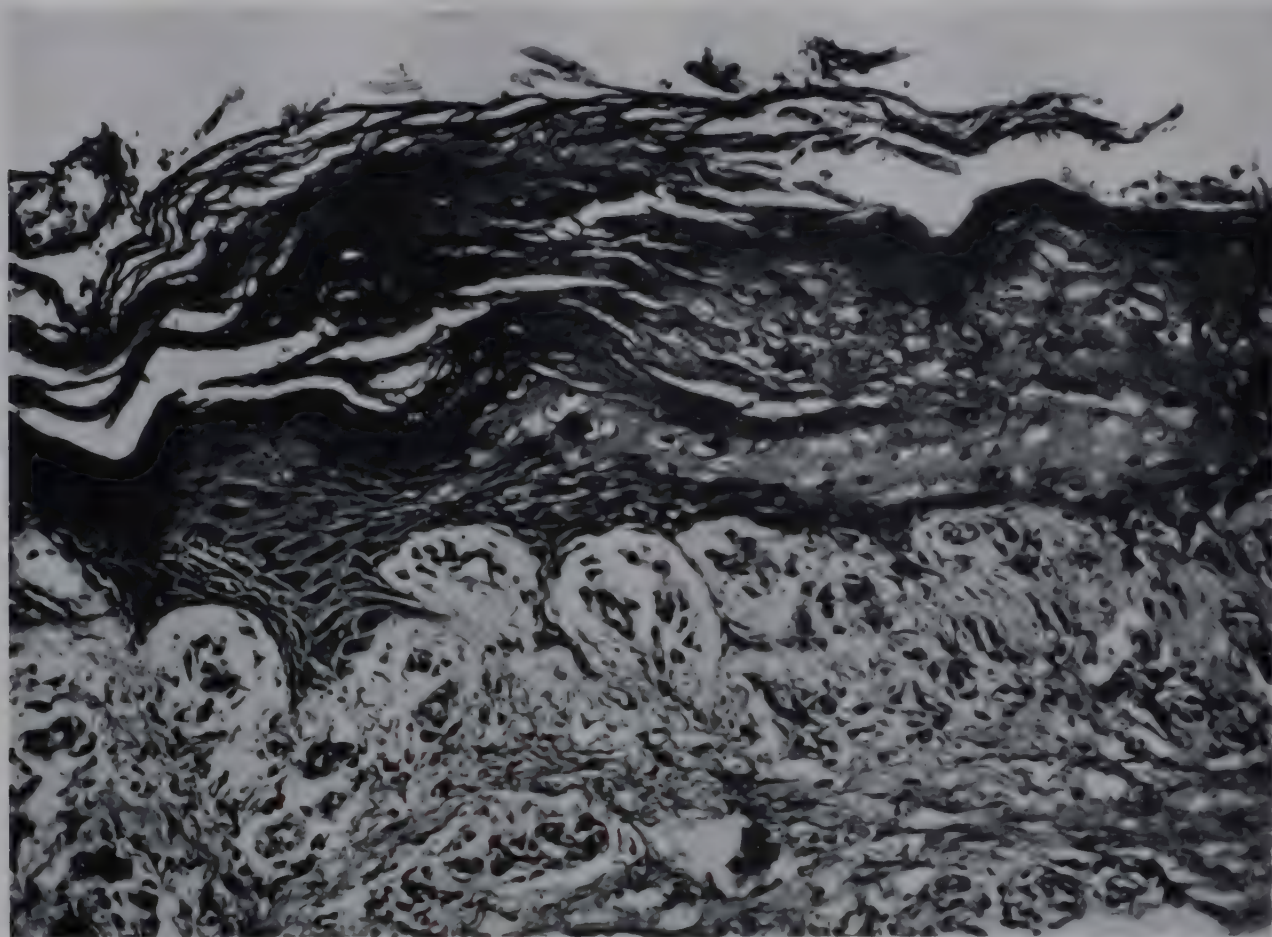


Fig. 275. Hyperkeratosis of epidermis and inflammation of dermis in pellagra. (From material reported by Moore, Spies, and Cooper: *Arch. Derm. & Syph.*, Vol. 46.)

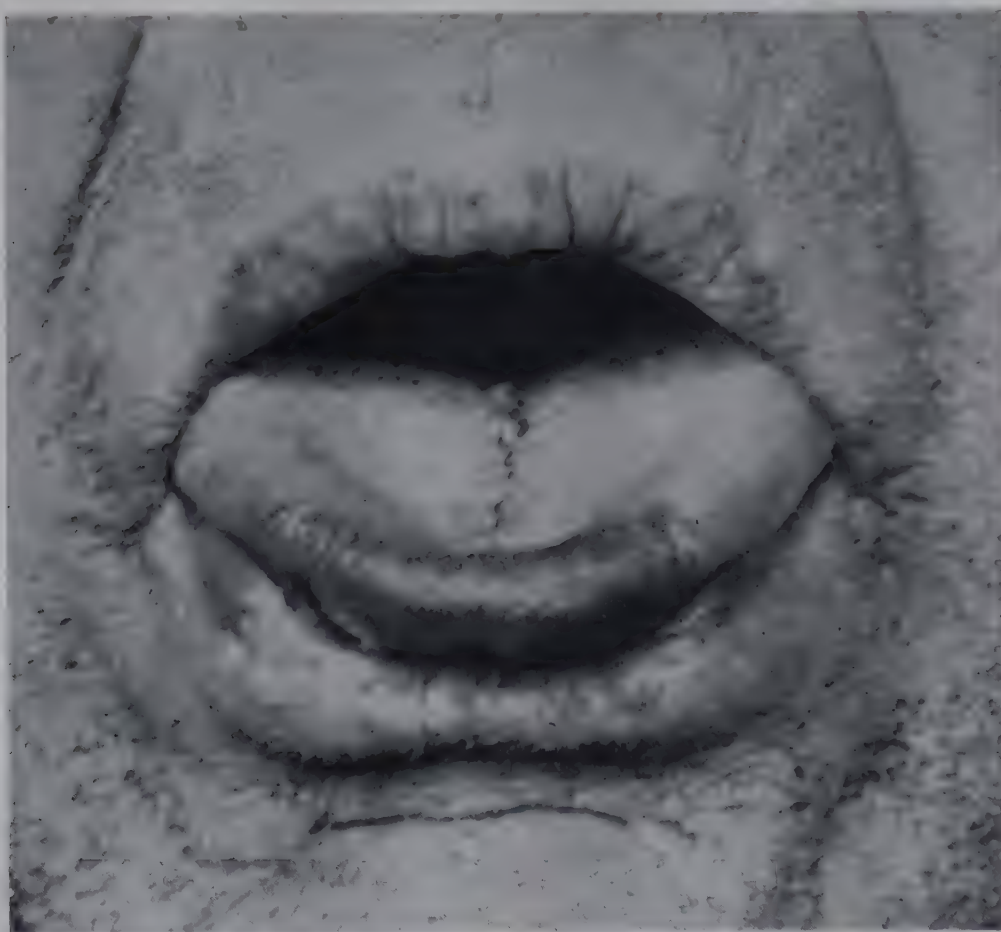


Fig. 276. Changes in the tongue in pellagra. (Photograph by courtesy of Dr. Tom Spies.)

cous membranes. In the brain there are few demonstrable histologic changes for many years, but eventually there is loss of ganglion

the solid viscera except for a terminal bronchopneumonia.

CLINICOPATHOLOGIC CORRELATION. The le-

sions of the skin and in the mucous membrane of the mouth lead to itching, burning, and at times pain. The inflammation in the gastro-intestinal tract is probably responsible for the diarrhea. The lesions on the skin are in general confined to the exposed parts of the body, and sunlight may be a localizing factor. Undoubtedly there are other factors, such as trauma and local tissue anoxia. It is possible that chronic alcoholism, aside from the inadequate intake of food usually associated with it, plays a role in precipitating clinical pellagra (Spies and De Wolf). It

Para-aminobenzoic Acid. Although this substance is necessary for the growth of certain bacteria, there is no evidence that it is an essential food substance for man. The effects reported are probably an influence on the intestinal bacterial flora (Bloomberg).

Pyridoxine. Pyridoxine, the eluate factor, or vitamin B₆, and the closely related compounds, pyridoxal and pyridoxamine, are concerned in the decarboxylation of tyrosine and as a transamination coenzyme. In rats deficiency leads to a desquamative dermatitis, and in rats, dogs, and pigs there may be epilepti-



Fig. 277. Cheilosis in ariboflavinosis. (Photograph by courtesy of Dr. Tom Spies.)

would also appear that pellagrins are more subject to infections and infestations, but this is not yet proved as specifically caused by lack of niacin. Of importance in the recognition of subclinical or chemical pellagra is the disturbance in the pigments of the body, leading to porphyrinuria. Achylia gastrica is possibly related to a macrocytic type of anemia, but all anemias in pellagrins do not have the same cause (Moore, Minnich, Vilter, and Spies).

Pantothenic Acid. Patients with pellagra have a decreased amount of pantothenic acid in the blood but no definite associated syndrome has been established. In chicks and rats a deficiency of pantothenic acid affects the skin and growth. There is some evidence that a deficiency in the rat causes graying of the hair—achromotrichia—but this relation has not been extended to man.

form convulsions. In man, it is useful as an adjunct to the other B vitamins in the treatment of pellagra (Spies, Bean, and Ashe) and of possible value in certain nervous and muscular disorders (Vilter, Aring, and Spies).

Riboflavin. *Ariboflavinosis.* PATHOLOGIC ANATOMY. Pathologic changes specifically caused by a deficiency of riboflavin, known as vitamin B₂ or G, are difficult to delimit in man since most persons showing a deficiency of riboflavin also lack other elements of the vitamin B complex. On the basis of a few controlled observations and comparisons with animal experiments, it may be reasonably assumed that a deficiency of riboflavin produces specific pathologic changes in the skin at the edges of the mouth and in the cornea. The lesions at the edges of the mouth first appear as a maceration of the epithelium,

followed by the formation of fissures and crusts. The crusts may be scraped off without producing bleeding, and there is little evidence of inflammatory reaction at any time. In more advanced stages the entire lip becomes slightly swollen and red. The term "cheilosis" is applied to the pathologic changes in the lips and adjacent skin (Fig. 277). In association with these lesions there is frequently a scaly desquamation of the epithelium in the nasolabial folds on the alae nasae, in the vestibule of the nose, and on the ears (Sebrell and Butler). The lesion in the cornea is essentially the growth of capillaries into and over the surface of the cornea and infiltration of leukocytes and lymphocytes into the cornea so that it is opaque (Sydenstricker, Sebrell, Cleckly, and Kruse). At the present time the possible changes in the nervous system, the anemia, and the lesions of the corporal skin cannot be accurately defined.

CLINICOPATHOLOGIC CORRELATION. The lesions at the edge of the mouth produce some discomfort. The corneal lesions are associated with itching, burning, photophobia, and dimness of vision. Most of these symptoms are directly referable to the increased opacity of the cornea from the infiltration of cells and growth of blood vessels, but it is possible that riboflavin may be an essential factor for the utilization of vitamin A in the synthesis of visual purple.

Choline. In view of the fact that considerable quantities of choline are present in yeast, and the fact that it has many of the characteristics of an accessory food factor, it is placed by some in the vitamin B complex. A diet deficient in choline, when fed to adult rats and dogs, leads to fatty degeneration of the liver (Best). In young rats, in addition to the fatty degeneration of the liver, there are enlargement, hemorrhage, and tubular degeneration in the kidneys (Christensen). In chickens and turkeys a perosis results. In all of these actions the deficiency of choline may be made up by the addition of methionine or betaine, indicating a cycle of conversion of these methylated compounds. It is possible that the choline in the diet is related to the quantity and activity of acetylcholine. Despite these clear-cut observations in animals, the establishment of a syndrome caused by a deficiency of choline in man has not been accomplished.

Avitaminosis C

Scurvy. In scurvy, which results directly from a deficiency of vitamin C, the basic defect is in the formation of fibrils in the intercellular matrix of the fibroblasts (Wolbach).

Pathologic Anatomy. The anatomic manifestations in any given case depend on two factors: growth of the part and the stress which is put upon the deficient tissue. Thus hematomas and osteoporosis are most prominent in children. The influence of stress is best illustrated by the observation that the signs and symptoms are most prominent in the arms of blacksmiths and in the legs of soldiers.

The lesions in the bones are commonest in the costochondral junctions, the distal end of the femur and the proximal end of the tibia and femur, and in the wrist, and are modified by stress (Follis). The distal end of the humerus and the proximal end of the ulna are usually spared. In the affected regions the formation of bone by endochondral calcification ceases, and the preexisting bone becomes rarefied and widened. The epiphysis is not affected but may become displaced. Microscopic examination reveals a rarefaction of the cortical bone, cessation of bony growth, and replacement of the normal metaphysis by a zone of collagen-poor connective tissue. In this connective tissue there are embedded fragments of densely calcified cartilage. The trabeculae of the primary and secondary spongiosa are narrow and there is no evidence of recently deposited osteoid. The myeloid and erythroid tissues of the bone marrow are inconspicuous and the marrow is largely replaced by a loose, almost mucoid mass of primitive fibroblasts. By serial study it can be shown that these fibroblasts are in reality osteoblasts (Daldorf). In the teeth the pathologic lesions are in the dentin. In children the dentin is not formed, while in adults there is resorption of it about Tomes' canals. Any new dentin which is formed is deficient and is known as osteodentin. In the pulp there are atrophy, dilatation of blood vessels, and degeneration of the odontoblasts. The tissues of the gingiva are swollen and may at times almost entirely cover the teeth. There is intense hyperemia and slight infiltration with lymphocytes. In the skeletal muscles there are fragmentation of the fibers and hyperplasia of the sarcolemmal cells. At

autopsy small petechiae or large foci of hemorrhage may be found in the skin, in the muscles, in the periosteum, in the serous membranes, and in the solid viscera. In general, the gastro-intestinal tract is spared. There is atrophy of the adrenal cortex and of the lymphoid tissue generally. Chronic loss of blood through hemorrhage may result in hypertrophy and dilatation and fatty degeneration of the heart. The hypertrophy is more marked in the right ventricle (Erdheim). In addition to the small hemorrhages about the

(Crandon, Lund, and Dill). The changes in the bone give characteristic modifications in the radiograph.

Vitamin C and Wound Healing and Infection. Although wounds fail to heal in manifest scurvy (Lund and Crandon), there is conflicting evidence on the relation of the plasma ascorbic acid level to the rate and efficiency of wound healing (Hartzell, Winfield, and Irvin). In most infectious diseases there is a depletion in the stores of vitamin C and this may influence the course of healing

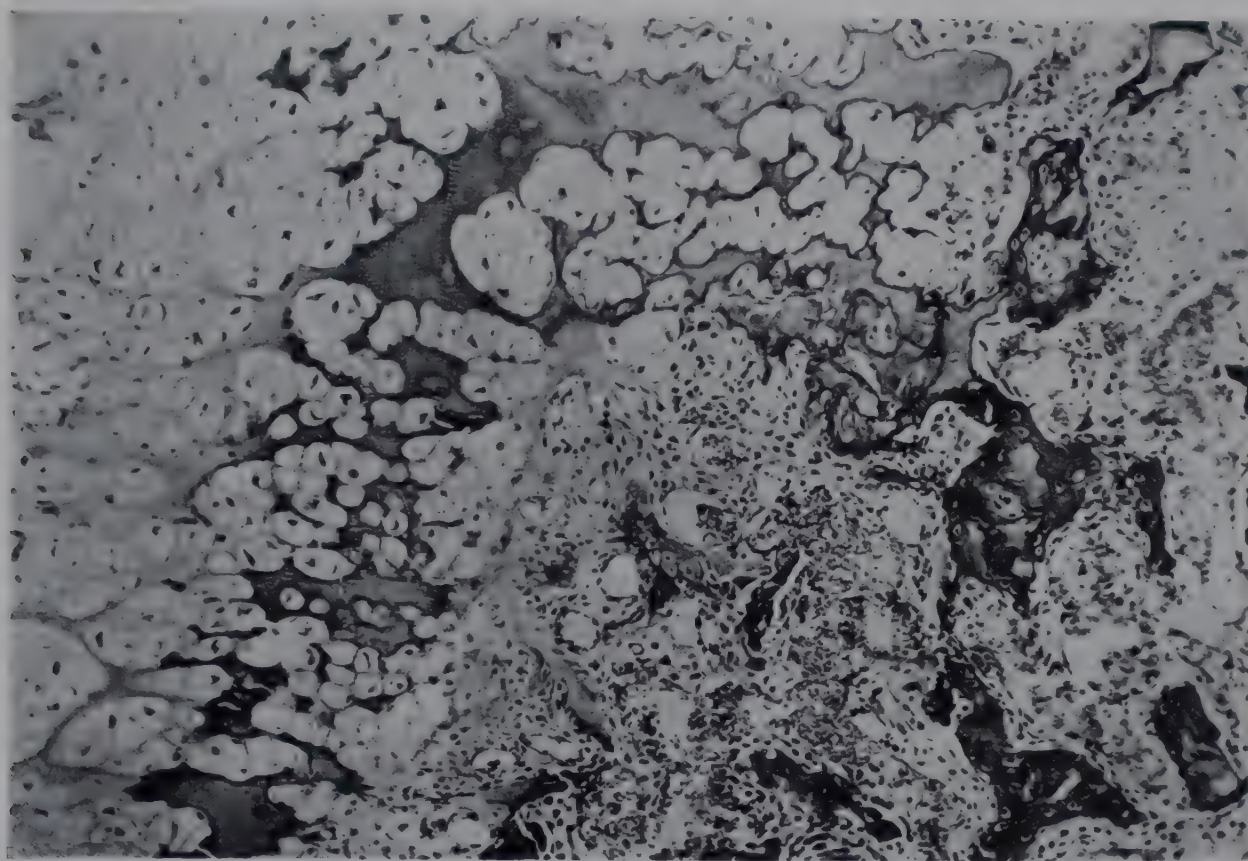


Fig. 278. Scurvy. (Armed Forces Institute of Pathology, Neg. No. 74147.)

hair follicles in the skin there is also slight hyperkeratosis immediately about the emerging hair.

Clinicopathologic Correlation. Aside from the manifest evidences of hemorrhage, and pain when the hemorrhage is into the periosteum or some other sensitive structure, there are few symptoms of scurvy. The pathologic changes in the muscles probably account for the general fatigue and weakness. The resorption of bone and the deficient formation of dentin may in extreme cases lead to looseness of the teeth. The atrophy of the bone marrow is responsible for the leukopenia and at times for the anemia, although the latter is probably caused by hemorrhage or a concomitant iron deficiency. During periods of depletion vitamin C is first lost from the plasma and last from the white blood cells

(Sweaney, Clancy, Radford, and Hunter). Vitamin C may be protective against hepatic damage (Beyer).

Avitaminosis D: Osteomalacia—Rickets

Osteomalacia. *Pathologic Anatomy.* The changes in the bones in osteomalacia are most prominent and advanced in the pelvis. In general, there is an approximation of the ischial tuberosities with contraction of the pelvic outlet. The inlet of the pelvis may or may not be contracted. The sacral curvature may be exaggerated or irregular. The vertebral column is shortened and there is usually a prominent lordosis. The long bones of the extremities, particularly of the lower extremities, are bowed, with a convexity laterally, or show

irregular curvatures. The individual bones are of approximately normal size, although when there is an associated general malnutrition the bones are decreased in size, and are more porotic than in the usual case of osteomalacia (Fig. 279). The bones vary from a slight decrease from normal consistency to an almost complete loss of calcium salts, so that it is possible to tie a bone such as the femur into a knot. On section no sharp distinction between the cortex and the medulla can be seen, and the entire bone is converted into a fairly uniform fibrous mass, devoid of individual

istic waddling gait or a complete inability to walk. The approximation of the ischial tuberosities and stenosis of the pelvic outlet renders delivery of a fetus, or even coitus, impossible. The depletion of calcium, despite the hyperplasia of the parathyroid glands, leads to repeated attacks of tetany. The slight fever present in most cases cannot be explained (Maxwell and Mills).

Causal Factors. The remarkable response of osteomalacia both clinically and pathologically to the administration of vitamin D clearly indicates that a deficiency of this sub-

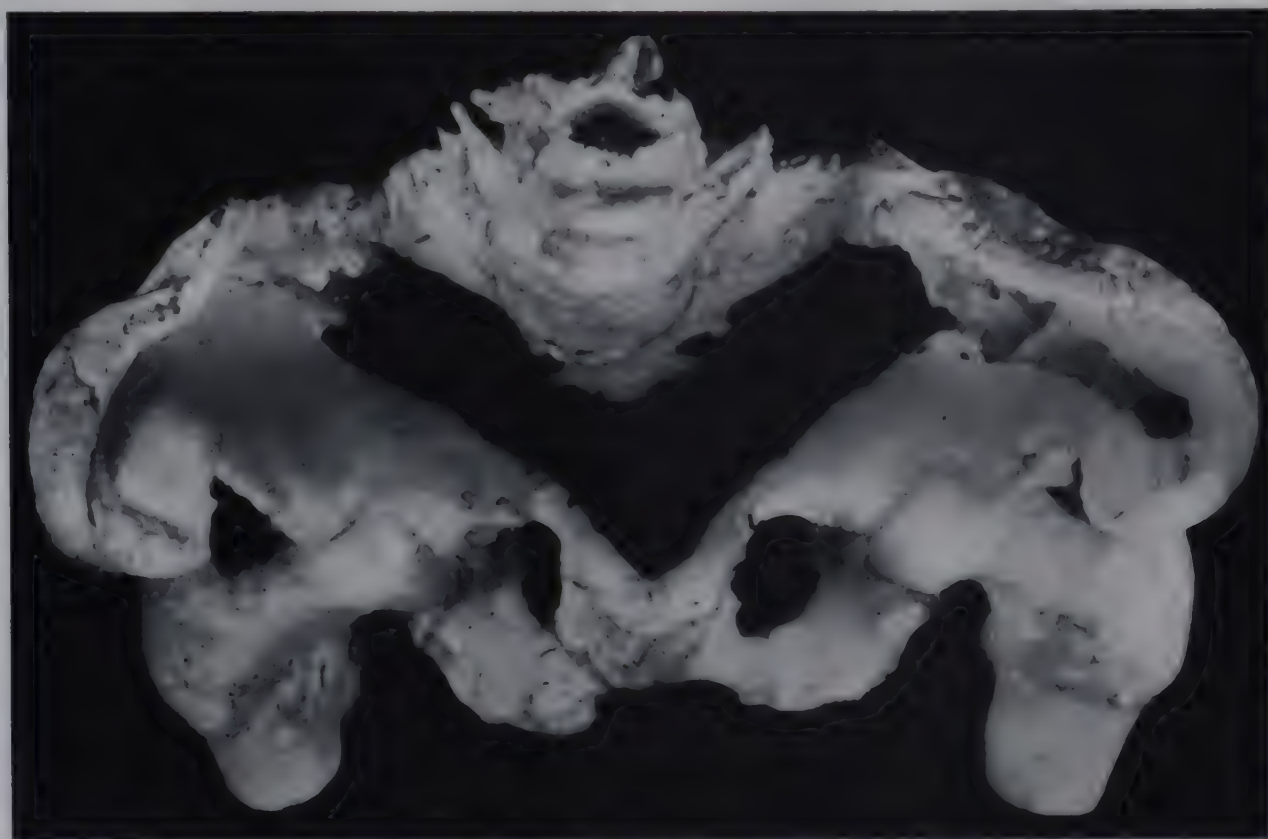


Fig. 279. Pelvis in osteomalacia.

trabeculae. The microscopic picture strikingly resembles that of rickets. There is a great excess of primitive osteoid, devoid of calcium. Some of the masses of osteoid resembling trabeculae may be surrounded by osteoclasts, suggesting resorption of the fibrous matrix as well as the calcium. Osteoblasts are numerous (Korenchevsky). The parathyroid glands are enlarged and are made up for the most part of clear cells (Bauer). The bones of an infant born of a mother with osteomalacia show the same changes, but to a limited extent.

Clinicopathologic Correlation. The changes in the bones lead to pain, most prominent in the back and in the legs. The softening of the vertebral column, of the pelvis, and of the femurs, and the weakness of the muscles and atrophy of the muscles, lead to a character-

istic waddling gait or a complete inability to walk. There are, however, many other contributing factors, such as hygienic and social conditions and sexual factors. It is most common in pregnant and lactating women, but may occur in men, especially during the decade following puberty. Its high incidence in India is probably directly attributable to deficient diet, plus the prohibitions of Mohammedanism that prevent women from being exposed to sunlight. Its prevalence in China may be attributed to the fact that Chinese women are often virtually starved during the last two months of pregnancy.

Hunger Osteomalacia. In the countries of central Europe, particularly Austria, during and after World War I there was a striking increase in the incidence of osteomalacia in postpuberal boys and in women, apparently

resulting from starvation (Medical Research Council, Partsch). There was of course a similar increase in all vitamin deficiency diseases.

Rickets. Rickets is a specific disease caused by a disturbance in the metabolism of cal-

costochondral junctions, the lower end of the radius and ulna, and the upper end of the tibia. The region of the metaphysis is enlarged and easily fractured. On section the cartilage immediately adjacent to the shaft of

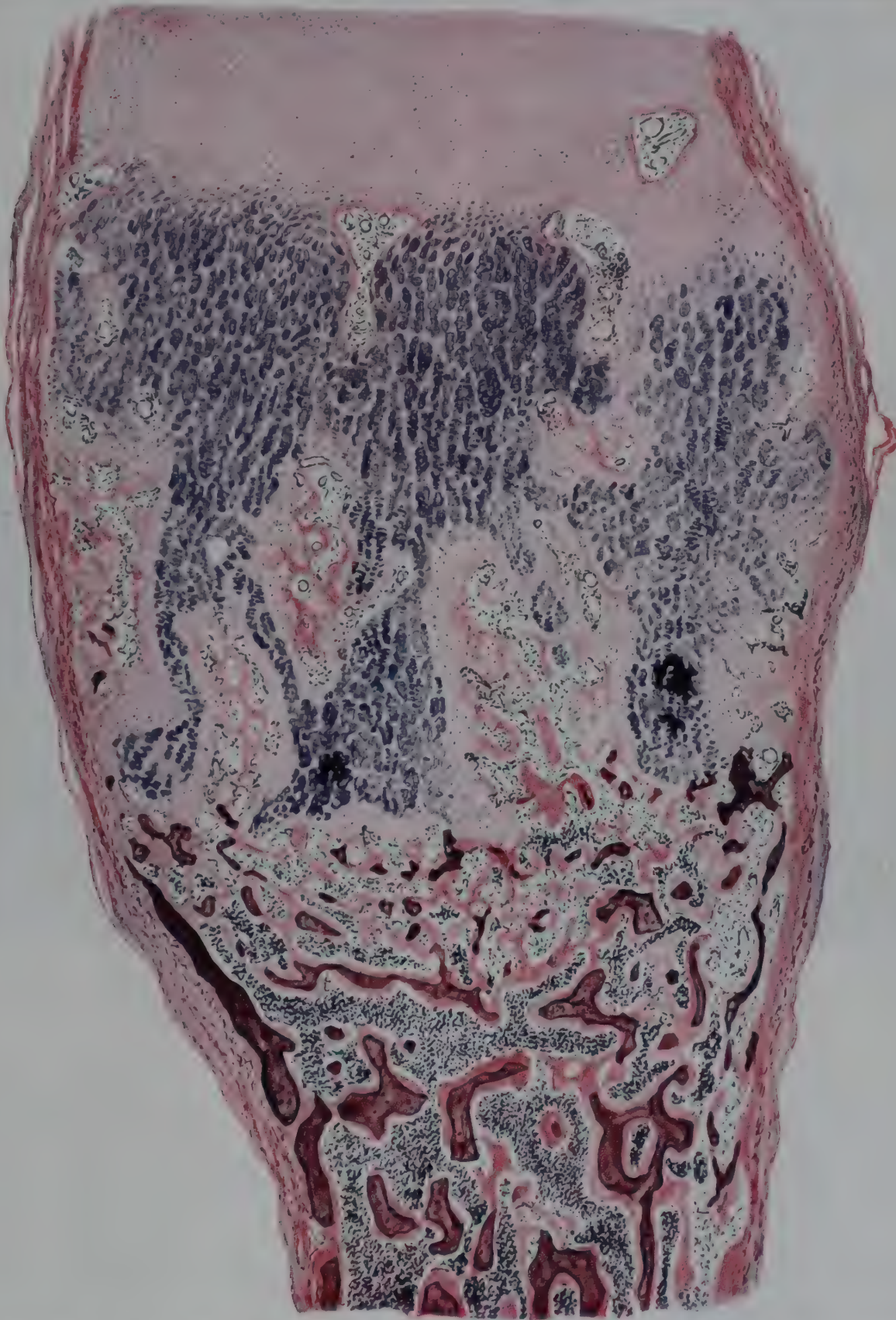


Fig. 280. Rickets: Rib at site of line of ossification. The preparatory zone of cartilage is irregularly invaded by perichondral and marrow vessels. Calcification of cartilage lacking, except in two or three foci. Invading blood vessels surrounded by osteoid tissue. Lamellae of bone remain partly covered with osteoid tissue. (MacCallum.)

cium and phosphorus, mediated by vitamin D, and affecting primarily the formation of bone.

Pathologic Anatomy. In the bone the pathologic changes are most prominent in those regions where the bone is growing rapidly, the

the bone is greatly increased and is the cause of the enlargement of the region (Fig. 280). The cartilage is blue and slightly translucent, in contrast to the gray or grayish blue, opaque resting cartilage about epiphyses. The line at

the junction between the cartilage and the bone is irregular and there are numerous vascularized foci extending into the cartilage from the primitive marrow. The zone of calcified cartilage, seen grossly in a normal bone as a light yellow or yellowish white zone, is entirely absent. The cortex of the diaphysis is decreased in thickness and in consistency. In the flat bones of the head, and in other places where there is membrane bone, the consistency is reduced and the distinct trabecular architecture is slightly obscured. In the parietal bones this lesion is especially conspicuous and is known as *craniotabes*. Lesions in other organs of the body are minimal. In most cases

is subjected. In the marrow there is a moderate deficiency of the blood-forming elements and replacement by either fibrous tissue or primitive osteoid.

In the process of healing, the excessive proliferate cartilage is quickly destroyed by invasion from the marrow, and calcium is deposited at the line of provisional calcification. This calcium is visible on the x-ray plate and the general phenomenon is known as the "line test for the healing of rickets" (Hess; Park; Schmorl).

HISTOGENESIS. From serial studies in experimental animals it is possible to arrange chronologically the various histologic features

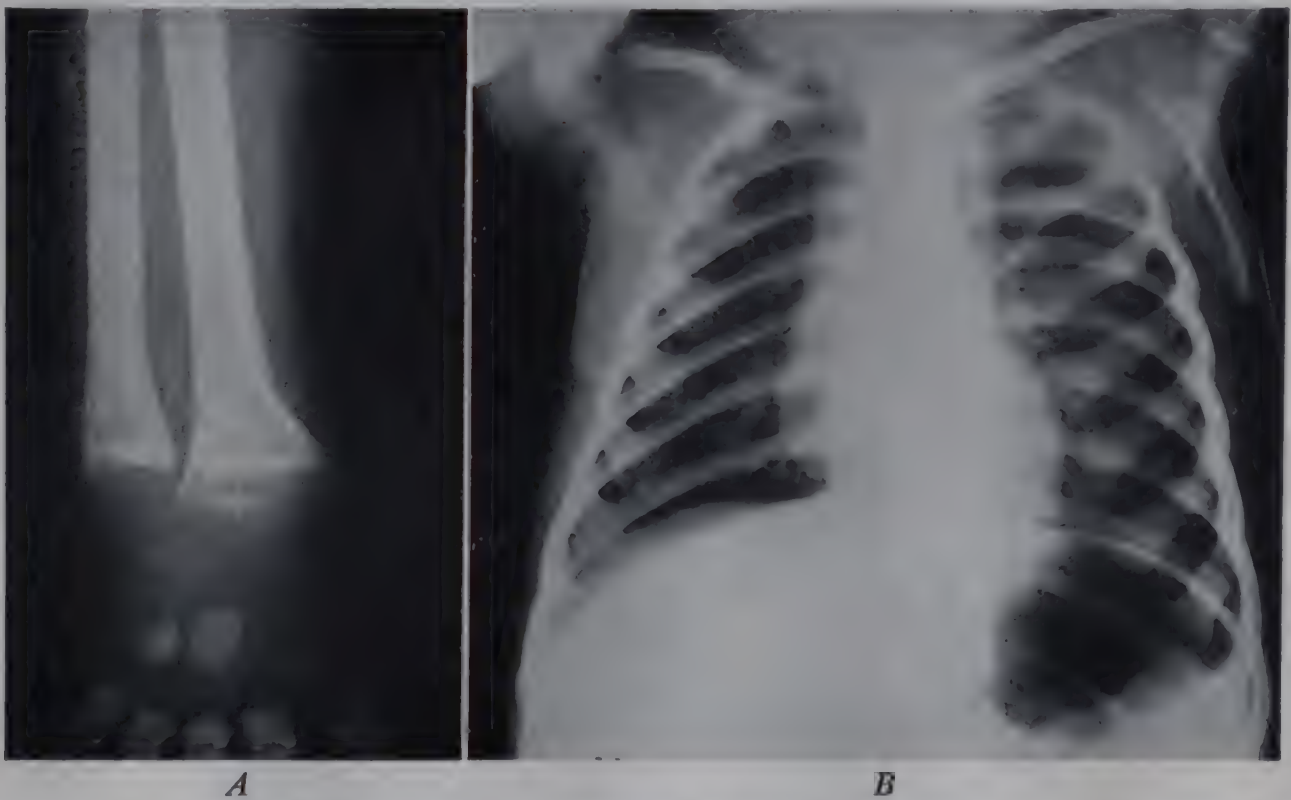


Fig. 281. Rickets. *A*, Wrist. *B*, Enlarged costochondral regions. (Armed Forces Institute of Pathology, Neg. No. 73960.)

the parathyroid glands are enlarged to two or three times normal size (Ham, Littner, Drake, Robertson, and Tisdall). The spleen and lymph nodes generally are larger than normal, soft, and show hyperplasia.

Microscopically the great increase in the zone of proliferate cartilage is immediately apparent. The columns of cartilage cells are no longer regular but are in complete disorder. Tongues of cartilage extend into the primitive marrow, with corresponding long or short projections of the marrow into the cartilage. In the primary spongiosa the trabeculae are broad, and on one or both sides there are excessive deposits of uncalcified osteoid. These deposits in general are arranged in accordance with the stress to which any given bone

described above. The initial change is a deficiency in the zone of provisional calcification. Shortly thereafter the trabeculae of cartilage are compressed and fractured. The cartilage continues to proliferate at the usual rate and therefore accumulates to produce the enlargement of the epiphysis. Finally there is invasion of the cartilage by vascularized marrow, both from the diaphysis and through the cartilage canals extending from the perichondrium. From this analysis it is clear that the basic defect in rickets is the lack of provisional calcification, traceable to a deficiency of calcium in this area (Park).

Clinicopathologic Correlation. Rickets is more common in colored than in white children, probably because of the poor utilization

of ultraviolet rays from the sun by pigmented skin. Rickets is more severe in rapidly growing children for the same reason that it attacks the more rapidly growing bones. The disease does not appear for some weeks or months after birth and congenital rickets has never been observed (Schmorl). The accumulation of proliferate cartilage is responsible for the enlargement of the epiphysis and for the rachitic "rosary." The reason for the general softening of the bones is not quite clear. Careful morphologic studies reveal no halisteresis and no abnormal destruction of pre-existing bone. The explanation is probably to be found in the replacement of bone by uncalcified osteoid in normal turnover. Clinically it is manifested by the softening of the skull bone, producing craniotabes and the typical "square head," by collapse of the thorax, by compression and curvature of the spine (kyphosis and scoliosis), and by bowing of the legs. The pelvis may collapse so that the anterior-posterior diameter is less than normal and the promontory of the sacrum extends far forward. The iliac bones are short, because of failure of growth, and thus the typical flat pelvis of rickets appears. The enlargement of the abdomen is difficult to explain except by the assumption that rickets is associated with atony of the abdominal and intestinal musculature. At autopsy extreme dilatation of the intestine is seen (Hess).

Late Rickets. Rickets is typically a disease of infants, but in some regions it develops in children from twelve to twenty years of age, and is known as late rickets. Since the bones are not growing rapidly, the pathologic changes are similar to those in osteomalacia (Brakeley).

Effects of an Excess. Excessive doses of vitamin D, especially if there is a high mineral diet, lead to metastatic calcification in animals (Shohl, Goldblatt, and Brown) and in man (Mulligan).

Avitaminosis E

The vitamins E are alpha, beta, and gamma tocopherol and are found particularly in vegetable oils and green leaves.

In male rats deficiency leads to irreversible degeneration of the germinal epithelium of the testis. In female rats there is death and resorption of the fetuses in utero (Mason).

In a variety of species avitaminosis E produces a muscular dystrophy with degeneration of the muscle fibers (Pappenheimer). This lesion is probably related to the antioxidant activity of the vitamin.

Vitamin E will protect vitamin A and carotene from oxidation and hence the requirement of the latter is lower when E is adequate in the diet.

There is no clear evidence as yet that dietary deficiency of vitamin E is related to disease in man (Council Report). This is possibly because of its widespread distribution in food and its bacterial synthesis in the intestine.

Avitaminosis H

A deficiency of vitamin H, or biotin, may be produced by restriction of intake or by feeding of the antivitamin, avidin, contained in egg white. In chicks and rats there is a seborrheic dermatitis, and in rats in addition a denudation about the eyes. In man there are dermatitis, lassitude, muscle pains, and anorexia (Sydenstricker, Singal, Briggs, DeVaughn, and Isbell). Biotin is identical with respiratory coenzyme R (Gyorgy, Rose, Hoffman, Melville, and du Vigneaud).

Avitaminosis K

Pathologic Anatomy. Vitamin K mediates the formation of prothrombin and hence its absence leads to inadequate clotting and hemorrhages. The latter vary from petechiae to large hematomas and may occur in all organs, tissues, and body cavities, notably in the skin, muscles, alimentary tract, urinary tract, and brain. Blood vessels in and about the hemorrhages are irregularly dilated (Ferraro and Roizin).

Clinicopathologic Correlation. The two outstanding conditions caused by a deficiency of vitamin K are the hemorrhagic tendency in patients with obstructive jaundice, and hemorrhage disease of the newborn. In the former, the long-continued absence of bile from the gastro-intestinal tract prevents proper absorption of the vitamin, and a dangerous hypoprothrombinemia results. Other conditions which bring about hepatic injury may also cause hypoprothrombinemia. Prothrombin values of the newborn infant are only about

25 per cent of those of adults (Javert and Moore) or even lower. These values in all infants decrease during the first few days of life, and may reach the point where gross hemorrhage occurs. The administration of vitamin K to the mother or to the newborn infant in most instances will prevent or cure the condition (Waddell and Lawson; Maumenee, Hellman, and Shettles).

Avitaminosis P

Szent-Györgyi in 1936 observed that an extract of paprika and lemons would restore capillary fragility to normal when decreased experimentally in guinea pigs. Some have called this vitamin P. The active principle is rutin, a glycoside of quercetin.

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LXIX

Diseases Caused by Specific Deficiencies

In addition to the lesions and diseases caused by a deficiency of the vitamins discussed in the preceding chapter, there are other deficiency diseases. Our knowledge of these began in 1928 and is still incomplete. The lacking substance appears to be a protein or polypeptide, and in some it is possible that there is a multiple deficiency. The conditions so far established as belonging in this category are pernicious anemia and sprue.

Pernicious Anemia

The elucidation of the cause and pathogenesis of pernicious or megaloblastic anemia is one of the triumphs of modern medicine. The condition is frequently referred to as "Addisonian anemia," and on the continent of Europe as "Biermer's anemia." After Addison first described it many ideas of cause and treatment were proposed, but it remained for Whipple to lay the groundwork and for Minot and Murphy to apply his principles to the treatment of the condition and to the elucidation of the essential nature of the anemia. For these studies these three men received the Nobel Prize in medicine in 1939. The success of the treatment of pernicious anemia with liver, initiated by Minot and Murphy, is shown by the fact that few patients have died of uncomplicated pernicious anemia since 1930.

Pathologic Anatomy. One of the characteristic features of untreated pernicious anemia is the course of the disease, alternating between relapses and remissions. The pathologic lesions found in the viscera and in the tissues depend on whether or not the tissues are removed during a remission or a relapse.

Bone Marrow. During a relapse, the bone marrow, both of the trunk and of the extremities, is red and cellular. It is composed predominantly of megaloblasts with a few normo-

blasts. The myeloid elements are present in normal amounts or are slightly decreased in amount. In serial studies it can be demonstrated that before the onset of a clinical remission there are histologic changes in the marrow. The megaloblasts decrease in number and numerous more mature cells of the erythropoietic series appear—erythroblasts and normoblasts. Similarly, before the beginning of a relapse the megaloblasts increase in number. These histologic findings are paradoxical. During the time when there is anemia and the greatest demand for red blood cells, the bone marrow is relatively inactive, and is composed of immature cells. In a full remission the bone marrow is entirely normal, and the long bones of the extremities contain the usual fatty type of marrow (Peabody).

Other Organs. The liver and spleen are slightly to moderately enlarged and firm. The tissue may have a light rust-brown color. In the liver the hepatic cells are well preserved, but the Kupffer cells are conspicuous and are filled with numerous brown granules of hemosiderin. There is no increase of fibrous tissue. In the spleen the follicles are normal. The sinusoids are dilated and throughout the pulp there are many macrophages filled with hemosiderin.

In the fundus of the stomach the mucosa is thin and semiopaque, in contrast with the thick, translucent normal mucosa. The glands are decreased in number and are cystic, and acidophilic cells are almost entirely absent. The interstitial tissue is increased in amount and infiltrated with lymphocytes. There are no significant changes in the muscularis or in the sympathetic plexuses of the gastric wall. Similar, but less marked, changes are seen in the pyloric part of the stomach (Brown). These anatomic findings are at variance with the known occurrence of the intrinsic factor in

the pyloric part of the stomach of the hog (Meulengracht). In the remainder of the gastrointestinal tract there are nonspecific changes of acute and chronic inflammation (Brown).

The spinal cord is smaller than normal, especially in the regions of the dorsal and lateral columns. The columns of Goll and Burdach, and the direct and indirect pyramid tracts show degeneration of myelin and of the axis cylinders—a lesion known as sub-acute combined-system disease of the spinal

acid has no effect on the lesions of the spinal cord (Spies and Stone).

Clinicopathologic Correlation. In addition to the general changes seen in all of the anemias there are specific clinical signs and symptoms resulting from the disease of the spinal cord in pernicious anemia. These are, as would be expected, the result of loss of the posterior white columns—decrease or loss of vibratory and other proprioceptive senses—and of the lateral white column—paresthesias

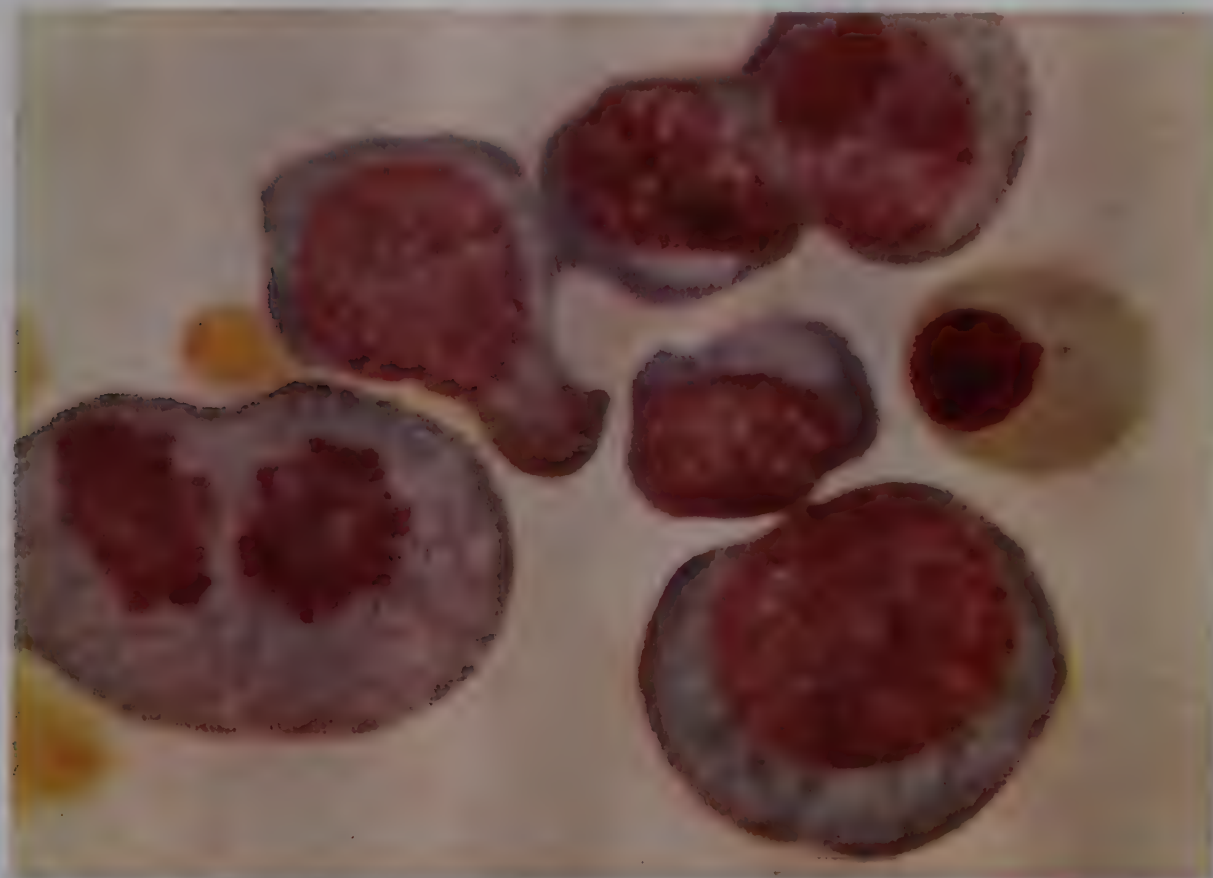


Fig. 282. Bone marrow in pernicious anemia, showing megaloblasts, early erythroblasts, and late erythroblasts. (Photograph taken by Dr. Malcolm Cook for Dr. Carl V. Moore.)

cord. There is clinical evidence of a peripheral neuritis, but this is not supported by anatomic studies.

The heart is dilated and hypertrophic, weighing from 400 to 600 gm. The muscle is pale and the characteristic markings of fatty degeneration are clearly discernible. The lymph nodes throughout the body are at times enlarged and contain small amounts of hemosiderin. Alterations in the other organs are inconstant, and are not related to the basic pathologic changes of pernicious anemia.

The Effect of Therapy with Liver. The administration of liver or folic acid brings about complete remission of the megaloblastic hyperplasia of the bone marrow. Liver has no influence on the chronic atrophic gastritis, and there are conflicting reports concerning the effect on the spinal cord (Davison). Folic

acid has no effect on the lesions of the spinal cord (Spies and Stone).

Types of Macrocytic Anemia. Early in the study of pernicious anemia it was recognized that macrocytosis was a distinct feature. However it soon became evident that macrocytosis occurred in anemias without megaloblastic hyperplasia of the marrow and without response to liver. The change in the marrow in these other types is normoblastic hyperplasia and is observed in leukemia, some hemolytic syndromes, hypothyroidism, sprue, and some aplastic and refractory anemias. Thus the concept of pernicious anemia primarily as a macrocytic anemia must be abandoned. On the other hand the anemias associated with megaloblastic hyperplasia of the marrow constitute an anatomic and etiologic group (Davidson and Davis).

General Concept of Megaloblastic Anemia.

During the 1920's the studies of Whipple and his associates showed that in dogs some foods were more efficacious than others in accelerating the synthesis of hemoglobin. Toward

growth consisting in a development of the primitive megaloblasts, and a failure of differentiation of the more mature red blood cells that normally get into the peripheral blood." Thus, on the basis of histologic

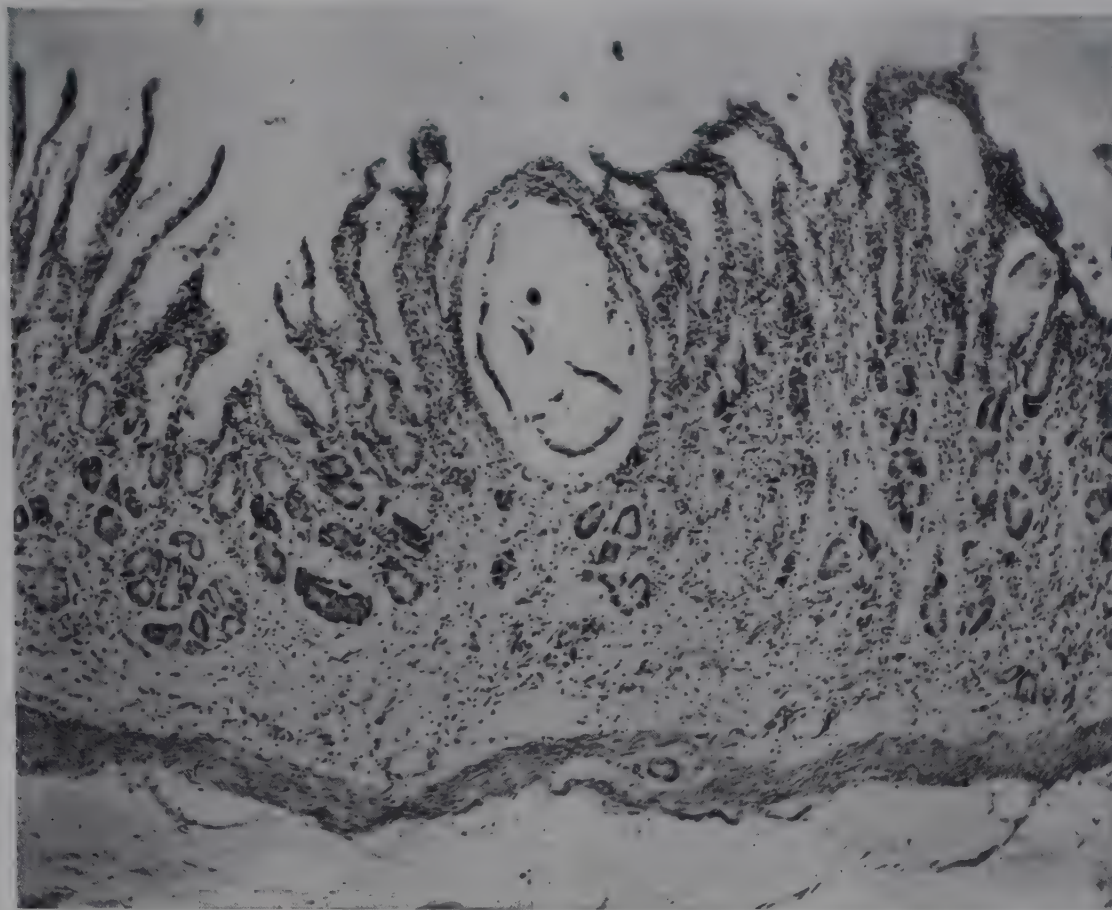


Fig. 283. Atrophy of the gastric mucosa in pernicious anemia.

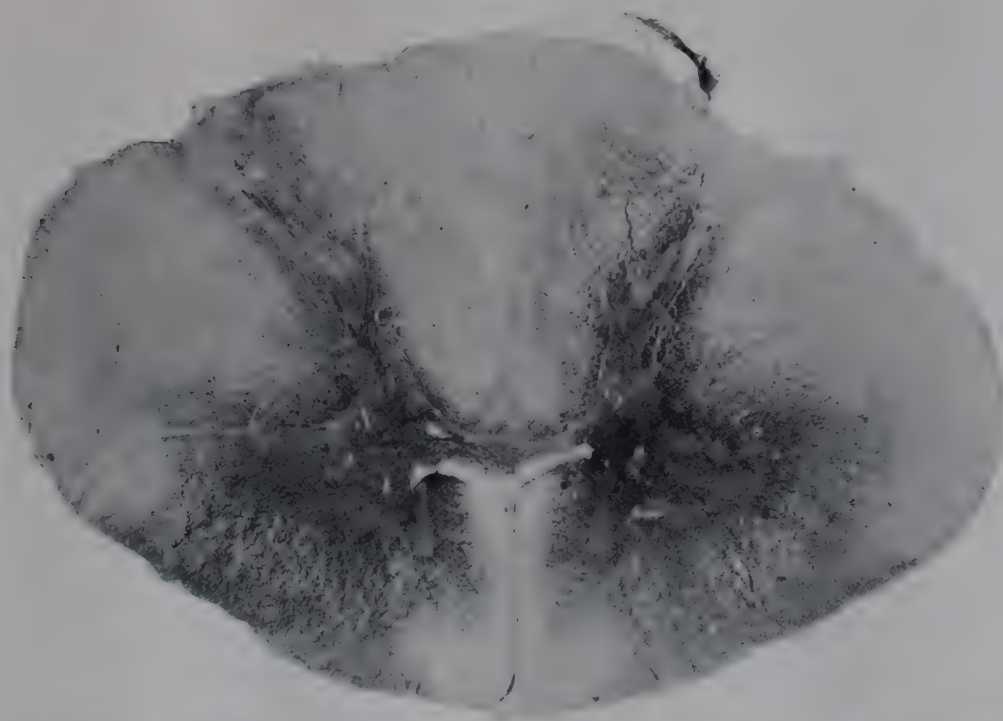


Fig. 284. Subacute combined-system disease of the spinal cord in pernicious anemia.

the end of the 1920's the careful histologic studies of Peabody showed that the bone marrow in pernicious anemia is hyperplastic. The conclusion of this brilliant investigator should be quoted: "The cause of the anemia would thus appear to be an abnormal type of cell

studies, Peabody concluded that the essential nature of the disease is lack of something that brings about full maturation of the red blood cells.

With this evidence, Minot and Murphy fed liver to patients with pernicious anemia and

secured prompt remission of the disease and maintenance of this remission for years. Castle and his associates went into the question of what this substance in liver is. Castle knew that atrophy of the gastric mucous membrane is associated with an achlorhydria, and that the disease could not be cured by the administration of any known constituent of the gastric juice—pepsin, renin, or hydrochloric acid. Despite this, he was convinced that the constancy of achlorhydria in pernicious anemia was concerned with the cause of the disease. He had further made the astute clinical observation that the diets of many patients with pernicious anemia are low in their content of meat. Accordingly Castle ate a quantity of beef, allowed it to digest in his own stomach, removed it with a stomach tube, neutralized it, and fed the resulting mixture to patients with pernicious anemia. They were promptly cured of their anemia. Control studies showed that beef muscle alone is inactive, that gastric juice alone is inactive, and that the gastric juice of a patient with pernicious anemia, when mixed with beef muscle, is also inactive. Only one conclusion was possible: that the normal gastric juice contains a substance which acts on another substance contained in beef muscle to give a third substance which is curative in pernicious anemia. Castle named the first of these “the intrinsic factor,” the second “the extrinsic factor,” and the third “the antianemic factor.” Since these classical studies, additional information has been secured to prove that the antianemic factor is stored in large quantities in the liver, and that it is carried by the blood stream to the bone marrow, where it is effective in bringing about full maturation of the red blood cells. In its absence the erythropoietic cells are held up in their development at the stage of the megaloblast.

With this information, various types of macrocytic hyperchromic anemia fit into a general picture. The same result may be secured from a deficiency of the extrinsic factor in the diet (pellagra), from a deficiency of the intrinsic factor caused by atrophy of the gastric mucous membrane (idiopathic pernicious anemia) or by destruction of it (carcinoma of the stomach), by lack of absorption of the antianemic factor in the small intestine (sprue and short-circuiting lesions of the intestine), from inability of the liver to store

and elaborate the antianemic factor (cirrhosis of the liver), or from interference with the utilization of the antianemic factor by the megaloblast (infestation with the fish tapeworm, and the rare instance of macrocytic anemia in pregnancy).

A substance called folic acid, which had been isolated from liver, yeast, and other sources, was known to possess bacterial-growth promoting properties when tested on *Lactobacillus casei*. It was then observed that folic acid was effective in rats made anemic by administration of sulfaguanidine. Trial in patients with pernicious anemia showed a prompt reticulocyte response (Spies).

Further attempts to purify the active principle in liver led to the discovery of vitamin B₁₂ which in doses of 3 to 6 micrograms will give a reticulocyte response (Rickes, Brink, Koninsky, Wood, and Folkers).

Thus, there are two pure chemical substances which will evoke a response in megaloblastic hyperplasia. Differences in effectiveness are noted and it is possible there are two forms of the disease; one is due to a deficiency of folic acid, and the other to a lack of vitamin B₁₂ (Dameshek).

Sprue

Typical sprue is essentially a disease of tropical countries, and it is customary to designate the disease as seen in temperate climates as “nontropical sprue.” The pathologic changes in the two differ quantitatively and to some extent qualitatively.

Pathologic Anatomy. In tropical sprue there is usually moderate or advanced emaciation. The abdomen is protruberant because of distention of the intestines. The wall of the intestine is thin, and the mucosa, especially of the small intestine, is atrophic, with few glands and inconspicuous lymphoid tissue. Parenchymatous organs are small and atrophic, but show no other consistent pathologic change. The appearance of the bone marrow varies with the presence and the degree of the associated anemia. In some instances it is atrophic, while in other instances there is the picture of megaloblastic hyperplasia, as seen in pernicious anemia. The tongue in general is atrophic and the normal rugal markings are inconspicuous.

In some cases of nontropical sprue there

is a small or large tumor blocking the entrance of the pancreatic duct into the duodenum. In others there is an obstruction in the mesenteric lymphatics, with great dilatation of the lymphatic vessels in the mesentery, in the mesenteric lymph nodes, and in the wall of the intestine. In general the mucosa of the small intestine is atrophic. Hemosiderosis of the liver and of the spleen has been reported. In the advanced cases of nontropical sprue there is osteoporosis of all of the bones, and megaloblastic hyperplasia of the bone marrow. There is likely to be some degree of atrophic stomatitis and glossitis. The parathyroid glands are increased in size, and are composed largely of chief cells. The histologic evidences of a deficiency of the fat-soluble vitamins are common.

Cause and Pathogenesis. From the pathologic findings outlined, it is evident that sprue is a complex deficiency state, of which some factors are known and others unknown. The most notable of the known factors are: the erythrocyte maturation factor, vitamins A and D, and fats and proteins. Despite adequate feeding of these substances the sprue syndrome develops or continues. The best hypothesis at the present time is that tropical sprue results from a lack of some unknown factor in the diet, or a failure of the intrinsic factor in the gastric juice, leading to progressive failure of absorption by the small intestine, particularly of fats and proteins. In nontropical sprue the absence of pancreatic juice, or the blockage of the mesenteric lymphatics for absorption, leads to the same result. So-called "idiopathic steatorrhea" is probably identical with nontropical sprue.

Clinicopathologic Correlation. The failure of elaboration or absorption of the erythrocyte maturation factor leads to megaloblastic hyperplasia of the bone marrow and a macrocytic type of anemia. Some of the signs and symptoms are therefore identical with those of pernicious anemia: weakness, changes in the motor and sensory system referable to subacute combined sclerosis, and atrophy of the tongue. The lack of absorption of fats is responsible for the typical fatty diarrhea. The deficient absorption of both fat and protein is the basis of the emaciation. Therapy with an active extract of liver is efficacious in most examples of tropical sprue, and in some of nontropical sprue (Snell).

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PART VI

DISEASES OF PREGNANCY AND OF
THE EXTREMES OF LIFE



Diseases Associated with Pregnancy

The pregnant woman may develop any disease. In fact it appears that she is more susceptible to some diseases such as recurrent appendicitis (Maes). Further, preceding disease, especially of the bony pelvis, may adversely influence the course of labor (Steele and Javert). Leiomyomas of the uterus show degenerative changes, probably because of pressure from the enlarging fetus (Randall and Odell). On the other hand, there is a group of conditions peculiar to the pregnant woman.

The Toxemias of Pregnancy—Preeclampsia and Eclampsia

About 7 per cent of all pregnant women suffer from some form of "toxemia of pregnancy." Of the three major causes of maternal mortality—infection, hemorrhage, and toxemia—the last is responsible for about one-fourth the deaths.

Toxemia is of two clinical types—preeclampsia and eclampsia. Each may be further classified on the basis of whether or not there is preexistent hypertension.

1. Without preexisting hypertension
 - a. Preeclampsia
 - b. Eclampsia
2. With preexisting hypertension
 - a. Without toxemia
 - b. With toxemia
 - (1) Preeclampsia
 - (2) Eclampsia

The relation of toxemia to hypertension is proved by two facts: first, that toxemia develops in 25 per cent of pregnant women with preexisting hypertension; and second, about 40 per cent of all women who have toxemia subsequently develop chronic hypertensive vascular disease (Chesley, Annitto, and Jarvis).

Pathologic Anatomy. Lesions may occur in the liver, kidneys, heart, and brain. There is great variability in the degree of involvement and uncertain correlations between severity of tissue change and clinical symptoms (Way).

Characteristically the liver is slightly enlarged and is mottled red and yellow. Over the surface and on the cut section there are large or small, irregular foci, 1 to 10 cm. in diameter, in which the tissue is red and friable. The intervening parenchyma is grayish yellow and softer than normal. Microscopic examination reveals a pathognomonic lesion immediately about the portal spaces. The sinusoids are dilated and filled with hyaline thrombi and degenerating red blood cells. The hepatic cells show all gradations of fatty degeneration and necrosis. There is no cellular infiltration except for a few leukocytes and monocytes associated with the thrombi. The hepatic cells of the midzone and the central zone are strikingly normal as compared with the cells of the peripheral zones. The blood vessels and bile ducts of the portal spaces are normal. The kidneys weigh 175 to 200 gm., and are yellowish red and firm. The capsule strips with ease, and the cortex is thickened to from 8 to 10 mm. There is not infrequently an associated pyelitis, evidenced by hyperemia of the mucous membrane of the pelvis and the filling of the pelvis with a thin cloudy fluid. Degenerative changes are observed microscopically in the epithelium of the renal tubules, either cloudy swelling, fatty degeneration, or frank necrosis. The glomeruli are hyperemic and the endothelial cells are swollen. It is probable that the thickening of the basement membrane described by some is related to chronic hypertension, not to the acute toxemia.

The heart is flabby and dilated. Degenerative changes, especially fatty degeneration

of the myocardial fibers and edema of the interstitial tissue, are seen. The brain is edematous; the convolutions are flattened; the sulci are narrow. Each small capillary is dilated and blood pours forth onto the cut section. Rarely there are small or large hemorrhages into the white matter, especially about the basal ganglia. There is little microscopic change other than edema.

Physiologic and Chemical Aspects. The outstanding chemical changes are (1) in the blood: an increase of uric acid, organic acids, and phosphorus, and a decrease of the carbon dioxide combining power and pH; and (2) in the urine a decrease in the urea nitrogen

a pregnant woman. In this view the cause is the same as that of all other hypertension, that is, a physiologic response of arterioles, probably vasospasm. The remote cause of the vasospasm may be ischemia of the uterus, not unlike the postulated ischemia of the kidneys in cardiac hypertension. Although pregnancy has an unfavorable influence on preexisting vascular disease, there is no evidence that it is caused by basic disease of the kidneys (Dexter, Weiss, Haynes, and Sise). This view is supported by the finding that the tubular excretory mass and the effective renal blood flow are normal in patients with hypertension and eclampsia (Wellen, Welsh, and Taylor). The

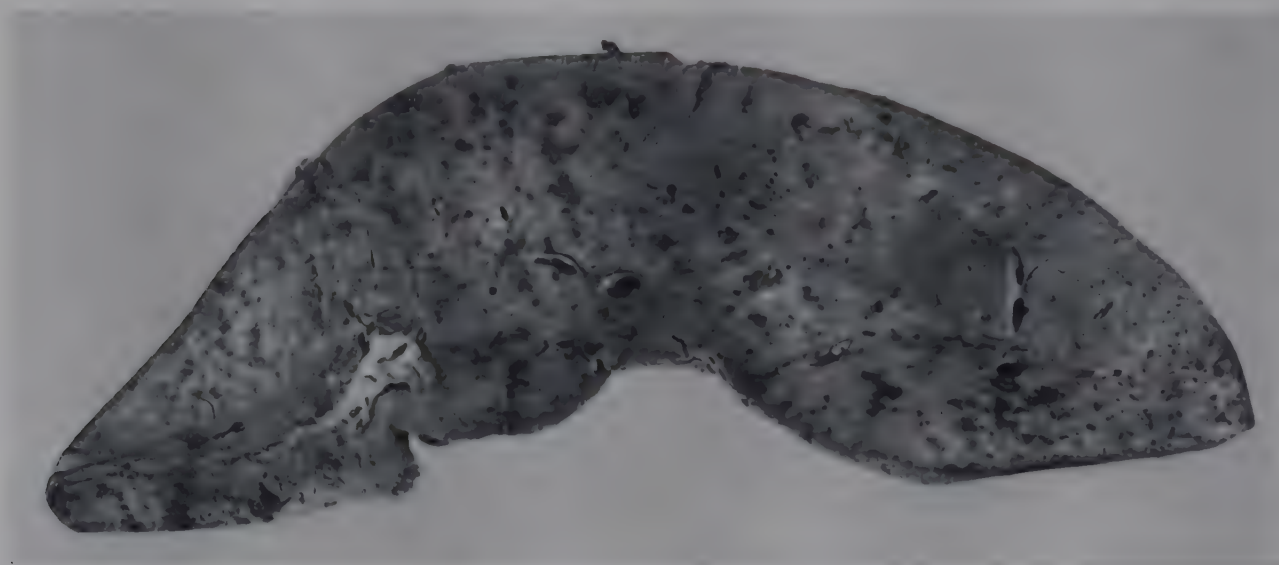


Fig. 285. Liver in eclampsia.

fraction and in chlorides. There is only rarely retention of the nitrogenous metabolites in the blood other than the uric acid.

Incidence. Eclampsia occurs in about one of 500 pregnancies, and in about 1 per cent of all hospital deliveries. It is commoner in primiparas than in multiparas, in twin than in single pregnancies, in pregnancy associated with hydramnios, in the spring than in other seasons, in China than in most other parts of the world, and in pregnancy resulting in hydatidiform mole.

Causal Factors. Many theories have been proposed to explain the cause of eclampsia, but none has been proved or generally accepted. Although there are no consistent changes in the endocrine glands, the demonstration of an early abnormality in the urinary excretion of hormones suggests an endocrine disturbance (Smith and Smith; Taylor).

The mass of evidence today suggests that eclampsia is in fact an acute hypertension in

most productive field for future investigation would appear to be a study of the basic physiologic processes in eclampsia.

Clinicopathologic Correlation. Studies so far conducted do not show a clear correlation between the amount of hepatic destruction and the degree of impairment of hepatic function. The renal changes are probably responsible for the albuminuria and possibly for the hypertension. The probability of a second attack of toxemia is higher than for the first, probably because chronic hypertension is a common sequela and chronic hypertension is a predisposing cause of toxemia. The retention of sodium is related to the retention of water and the edema.

The anatomic changes in a patient with pre-existing hypertension are those of chronic hypertensive vascular disease, benign or malignant, with the more acute alterations of eclampsia described in the preceding paragraphs.

Maternal mortality varies from 10 to 25 per cent, and the mortality of infants born of eclamptic mothers approaches 50 per cent.

Pernicious Vomiting of Pregnancy

Pernicious vomiting occurs in about one of each 150 pregnancies and is commoner in the upper social classes (Peckham).

Pathologic Anatomy. The characteristic pathologic changes are in the liver, which is normal or slightly increased in size, yellow, and soft. Either central necrosis or fatty degeneration, or a combination of the two, is found. In advanced cases the necrosis may include the midzone and spare only the most peripheral zone of cells. In the kidneys there are not infrequently cloudy swelling and necrosis of the epithelium of the proximal tubules, but the glomeruli are normal (Bell).

Physiologic and Chemical Aspects. In mild cases there is little alteration in the chemical constituents of the blood. In severe cases there is an increase of the nonprotein nitrogen, uric acid, urea, and sugar, a decrease in chlorides, and no change in the carbon dioxide combining power, all probably resulting from the associated dehydration and not from the primary disease. The same is true of the increased excretion of urinary ammonia (Peckham).

Causal Factors. The frequency of some degree of nausea and vomiting in all pregnant women suggests a relation to some physiologic alteration of pregnancy, possibly to the elevated chorionic gonadotropin in the early months.

Clinicopathologic Correlation. In most instances the nausea and vomiting are the only clinical changes, and they cannot be directly related to an anatomic lesion. If the renal changes are conspicuous, there is albuminuria, and, if severe, oliguria. If the vomiting continues, the secondary dehydration and emaciation may be more dangerous to life than the primary condition. Polyneuritis is related to vitamin B deficiency.

Lesions of the Placenta

Anomalies. A common anomaly of the placenta is separation into two or three lobes (Torpin and Hart). In the *circumvallate pla-*

centa a part of the decidua separates the margin of the placenta from the chorionic plate. There is a thick, white, opaque ring around the periphery of the placenta that limits the course of the fetal vessels (Hobbs and Price).

Abnormalities of Implantation and Separation. The placenta is normally implanted on the anterior or posterior surface of the fundus. If implanted lower, it frequently separates prematurely at the time of the dilatation of the internal os and is known as "placenta praevia." Premature separation of the normally implanted placenta is caused by hemorrhage into the decidua and myometrium. It occurs more frequently in patients with acute or chronic hypertension. In *placenta accreta*, the chorionic villi are attached directly to the myometrium without the intervention of the endometrium and decidua. The placenta does not separate easily at delivery, and hysterectomy may become necessary in order to stop bleeding. The cause is apparently a preexisting scar of the endometrium (Irving and Hertig).

Vascular Disturbances. As the placenta ages in the latter months of pregnancy, fibrin is deposited over the villi or beneath the syncytia, or blood in the maternal sinusoids may clot. In some instances the block of maternal nutrition to the placenta may lead to the formation of a true infarct.

Inflammations of the Placenta. In addition to rare examples of involvement of the placenta by pyogenic bacteria, tuberculosis (Schaefer) and syphilis (Dorman and Sahyun; McCord) have been described.

Benign Tumors. Benign tumors of the placenta are rare, and of all those observed the angioma is by far the commonest. The angioma is a spherical or lobulated mass, varying from 5 mm. to over 20 cm. in diameter. It is firm and dark red, and the structure is slightly reticulated. The structure varies from a richly vascularized tissue to a type in which the chorionic stroma is more prominent. The small capillary vessels are lined by a single layer of endothelium, while the stromal cells have the typical structure of the stroma of the normal chorion. Areas of hemorrhage, edema, and necrosis are not uncommon. Angioma of the placenta is not infrequently associated with hydramnios. So far as can be determined, this tumor has no influence on the fetus (Marchetti).

Hydatidiform Mole

Pathologic Anatomy. The entire placenta is converted into a bulky mass of cysts. Usually no fetus is present. Microscopic examination shows three characteristic features: proliferation of the trophoblast, hydropic or mucoid degeneration of the stroma of the villi, and scantiness of the blood vessels. The degree of trophoblastic proliferation is variable, and when it is extensive there follows invasion of the blood vessels of the uterine wall. Some investigators designate the condition as "malignant hydatidiform mole" or "chorioadenoma destruens." There are rarely metastases outside the uterus but occasionally

sional villus with microscopic cystic change, but the fully developed disease occurs only in about one of every 200 pregnancies. The cause is unknown, but it is probably a defect in the ovum.

Clinicopathologic Correlation. Most moles occupy a larger mass than the normal placenta and embryo, hence the uterus is larger than would be expected for the estimated time of gestation. Implantation is inadequate, and there is frequently intermittent or continuous uterine bleeding. The prognosis is good after thorough curettage, or, if the vessels of the uterine wall are invaded, after hysterectomy. Toxemia of pregnancy is commoner in a woman with a mole than in one with a normal

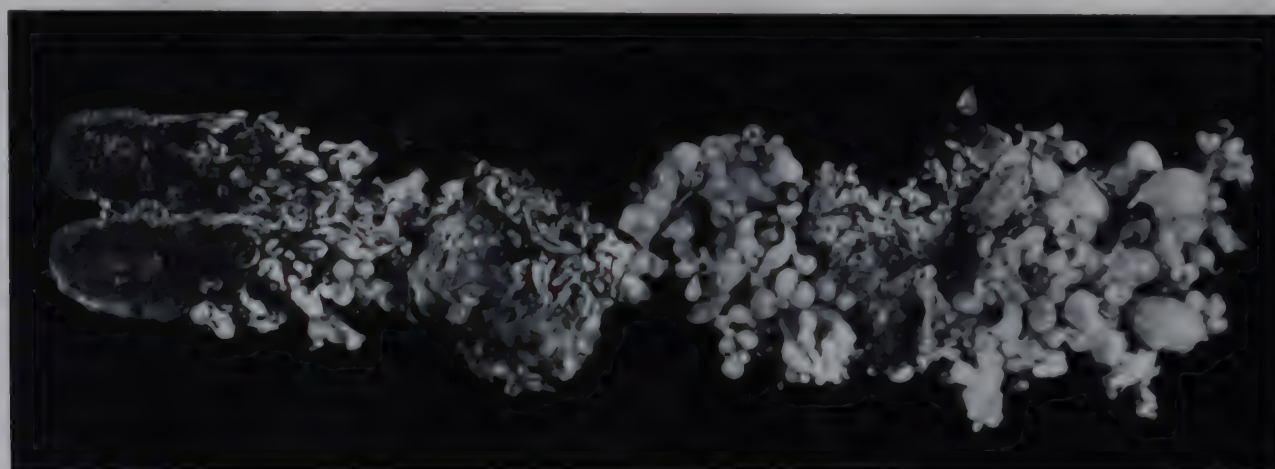


Fig. 286. Hydatidiform mole.

metastases to the lung occur. Degeneration of the stroma of the villi is prominent. A part or all of the stroma of the villi is converted into a single or multiloculated space, filled with a clear limpid or viscid fluid. There are few blood vessels within the villi.

Ovarian Changes. In about 60 per cent of all hydatidiform moles there are characteristic lutein cysts of the ovaries. The cysts may reach large size, and be uniloculated or multiloculated. The contained fluid is clear, and the wall is composed of luteinized thecal cells and fibrous tissue.

Endocrine Relations. The fluid within the cysts of the villi and the urine of the patient contain excessive amounts of chorionic gonadotropin, usually over 100,000 mouse units per liter. This fact is of great importance in establishing a clinical diagnosis. The gonadotropin is probably responsible either directly or indirectly for the ovarian changes (Cosgrove).

Incidence and Causal Factors. Careful histologic study of all placentas shows an occa-

fetus. The rare metastases usually regress after removal of the uterus.

Choriocarcinoma

Pathologic Anatomy. The typical choriocarcinoma is a raised, somewhat circumscribed nodular tumor in the fundus of the uterus, composed of dark-red, soft fibrous tissue. The neoplastic tissue extends well into or through the myometrium, and the larger blood vessels are filled with tumor tissue. Two cellular types, cytotrophoblasts and syncytiotrophoblasts, are intermixed in variable proportion. The malignant cells invade the blood vessels, and penetrate between the muscle fibers of the myometrium. Mitoses are usually not abundant, and the degree of anaplasia is variable. Hemorrhage and necrosis of large or small foci are common. Lutein cysts of the ovaries similar to those of hydatidiform mole are found in about one-third of the cases.

Metastases are the rule, and are most frequently seen in the lung and in the wall of the

vagina. Less common sites are kidneys, spleen, ovary, liver, and brain.

Hormonal Relations. As in the mole, there is urinary excretion of excessive amounts of chorionic gonadotropin, as well as the changes of pregnancy in the pituitary (Cosgrove).

Incidence and Causal Factors. About 50 per cent of all choriocarcinomas follow hydatidiform mole. Twenty-five per cent occur after abortion, and 25 per cent after normal term delivery. The average age is thirty-three years.

ovaries, and in the testes. The latter two are probably specialized types of teratoma.

Ectopic Pregnancy

By "ectopic pregnancy" is meant a gestation in which the fertilized ovum implants at some site other than the usual one in the endometrium. The term includes tubal pregnancy, interstitial pregnancy, pregnancy in a rudimentary uterine horn, interligamentous pregnancy, ovarian pregnancy, and abdominal pregnancy. Ectopic pregnancy occurs in one

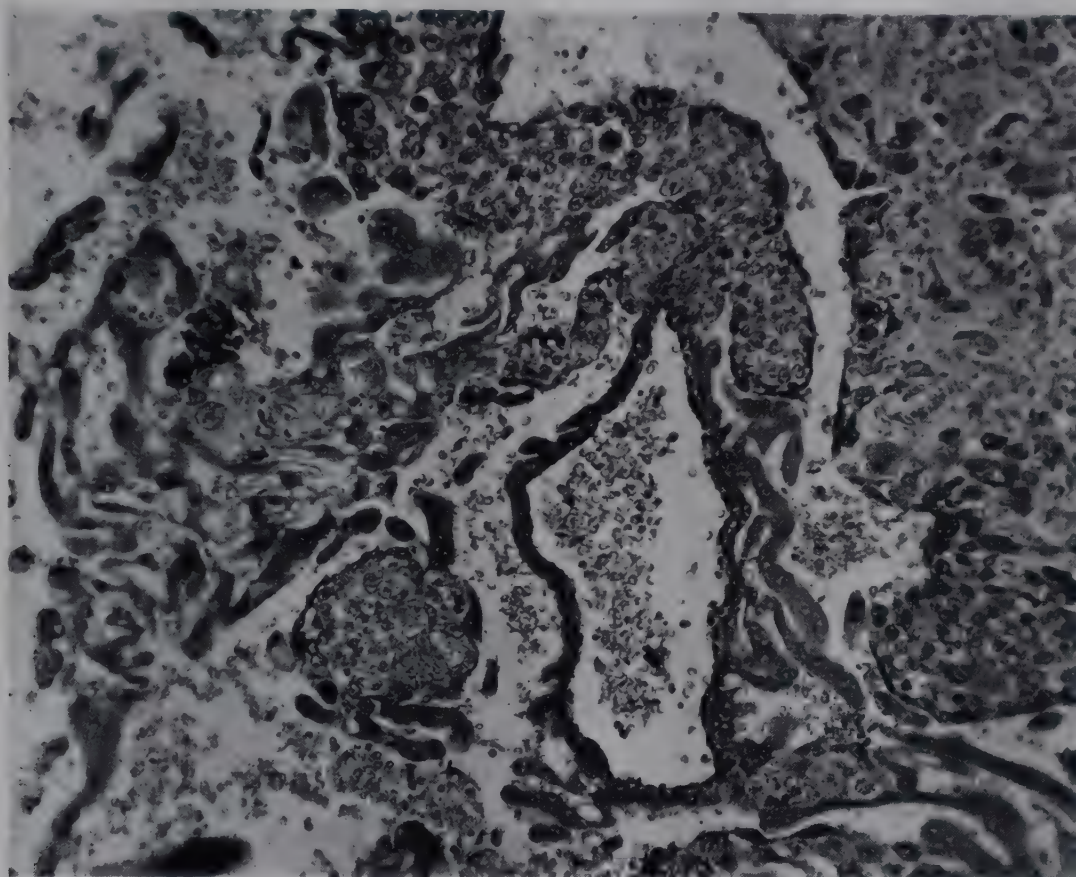


Fig. 287. Choriocarcinoma.

Clinicopathologic Correlation. Superficial necrosis of the tumor mass leads to vaginal bleeding and an offensive vaginal discharge. The choriocarcinoma produces few compelling clinical signs or symptoms, and the metastases to the vagina and the lung may be the first basis of complaint. The prognosis is not good, but a few cures have been affected by early surgical removal.

The differential histologic diagnosis between normal invasion of the myometrium by trophoblasts, invasive mole, and choriocarcinoma is extremely difficult. If any organized villi are present, the last diagnosis is probably not correct.

Ectopic Choriocarcinoma. Tumors identical with the uterine choriocarcinoma occur in the uterine tubes (Williams), in the

out of each 300 or 400 conceptions. It is commonest in the tube (Schauffler and Wynia).

Pathologic Anatomy. In tubal pregnancy the tube is enlarged, either diffusely or at one point, depending on the size of the fetus. Most specimens, when they come to the attention of the surgeon or the pathologist, have ruptured, and the result is a large rent at one point where the tube is of the largest diameter. On section the wall is seen to be extremely thin and to be invaded by the chorion. The lumen is filled with clotted blood, and careful examination may be required to demonstrate the fetus, which is rarely over 15 to 20 mm. in length. In the ovary a fully developed corpus luteum of pregnancy may be demonstrated, occasionally in the opposite ovary.

Termination of a Tubal Pregnancy. Because of the expanding force of the contained fetus, tubal pregnancies rarely progress beyond the third month. The fetus may be expelled into the uterus or into the peritoneal cavity, where, if it does not die, the placenta will grow and the pregnancy continue. Usually, however, there is hemorrhage into the chorion and the fetus dies. It may be completely absorbed or may mummify or calcify. The calcified fetus is known as a "lithopedion" (Scott and Manahan). It may be discovered many years after conception. The usual course of tubal pregnancy is the rupture of the tube with the tearing of large blood vessels. There is extensive hemorrhage into the tube or into the peritoneal cavity.

Reaction in the Uterus. Regardless of the position of the fetus, the endometrium usually undergoes a decidual reaction. On the death of the fetus the decidua separates and may appear in the vagina as a cast of the lining of the uterus, but histologic examination of curettings cannot be used as an infallible diagnostic test for ectopic pregnancy.

Causal Factors. The most important causal agent of ectopic pregnancy is chronic salpingitis. The fertilized ovum in passing down the tube enters a cavity from which there is no exit, and within a short time develops and implants in that spot.

Clinicopathologic Correlation. The general changes of pregnancy, such as suppression of menstruation, are the same in ectopic as in uterine pregnancy. Some time during the third month there is sharp abdominal pain, caused by the rupture of the tube, and within a period of hours or days there is sufficient loss of blood into the peritoneal cavity to produce profound anemia and shock. Careful studies have shown that bleeding from the uterus occurs only after the fetus has died.

Maternal Mortality

The term "maternal mortality" indicates the death rate among pregnant and puerperal women from causes directly or indirectly associated with the gravid state. In forty years the rate of maternal mortality in the United States has been reduced from over 10 per thousand live births to between 1 and 3. The actual figures and the relative distribution of causes vary, depending on location, whether or not a physician attended, and whether or not de-

livery took place in a hospital. In general, one-third of the deaths are related to uterine hemorrhage (Conn, Vant, and Cantor), one-quarter to toxemia, one-quarter to infections, and the remainder to miscellaneous causes, the most important of which is some type of heart disease (Jensen).

Abortion

It is customary to designate the loss of a fetus before the sixteenth week as an "abortion," between the sixteenth and twenty-eighth week as a "miscarriage," and after the twenty-eighth week as "premature labor." The criminal implications incorrectly conveyed to the lay mind by the word "abortion" limit its usefulness (Hertig and Sheldon). Abortion is usually caused by the death of the fetus. Miscarriage and premature labor may be the result of any one of a number of conditions. The cause may be found in either the mother or the child (Potter and Adair; D'Esopo and Marchetti). On an average, 70 out of every 100 conceptions proceed to viability; 10 are aborted during the first few months, 10 never implant, and 10 are so abnormal that pregnancy is not recognized. Thus, the recognized abortion rate of 10 per cent is only one-third of the actual.

Maternal Influences. In the category of maternal influences are systemic infectious diseases, chronic endometritis, congenital abnormalities of the uterus such as an infantile uterus, displacements of the uterus such as retroflexion and prolapse, and abnormalities of the decidua such as decidua polyposa. In habitual abortion it has been suggested that a deficiency of vitamin E, vitamin K, or the corpus luteal hormone is responsible. There is little evidence that there is an infectious abortion of women such as occurs in cows and in horses. In habitual abortion, there is evidence of a deficiency of the corpus luteum or thyroid or both.

Fetal Influences. In the category of fetal influences are infarction of the placenta, shortness of the umbilical cord, winding of the cord about the neck, pathologic ova (Hertig and Rock), and anomalies of the fetus incompatible with life (Potter). If the fetus remains in the uterus after death, there are maceration of the skin and autolysis of the tissues. If retained for years, the fetus is calcified.

The *immediate cause* of all abortion is

retroplacental hemorrhage. In 20,050 premature and term infants Stander reports a gross mortality of 750, including 484 deadborn and stillborn, and 286 live births with neonatal death.

Role of the Isoagglutinins. The theory that abortion might result from incompatibility of the major blood groups of the Rh factor between mother and fetus is not supported by statistical studies.

Pulmonary Embolism in Parturient Women

In addition to pulmonary embolism from thrombi in the veins of the pelvis and lower

Amniotic Contents. Steiner, Lushbaugh, and Frank have described the presence of squamous epithelium, mucus, meconium, and amorphous debris in the pulmonary capillaries of women who have died of so-called "obstetric shock" within the first few hours after delivery. Both the clinical and pathologic picture can be reproduced in experimental animals by the injection of amniotic fluid.

Diseases of the Lactating Breast

During pregnancy there are progressive enlargement of the breasts, increasing pigmentation of the areoli, and hypertrophy of the glands of Montgomery. The nipples become

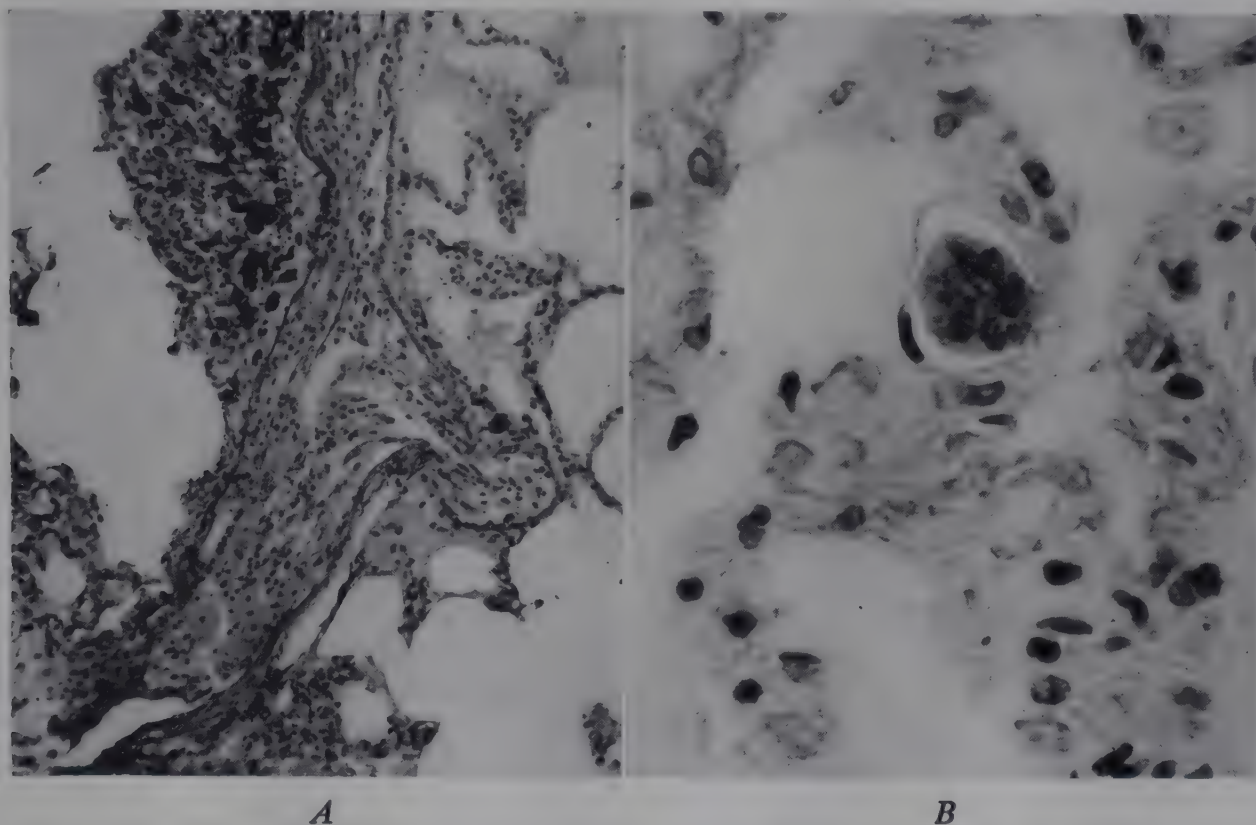


Fig. 288. *A*, Amniotic contents in a pulmonary artery (slide by courtesy of Dr. Paul Steiner). *B*, Giant cell in pulmonary capillary of a woman who died a few hours after delivery.

extremities, and air embolism from the opened uterine sinusoids, there are two special types of pulmonary embolism which occur in parturient and puerperal women: emboli of elements of the chorion and decidua, and emboli of the amniotic content.

Chorionic and Endometrial Elements. Histologic examination of the lungs during the first few days after parturition frequently reveals many large cells with hyperchromatic nuclei completely occluding the pulmonary capillaries. It is believed that these are decidual cells or possibly syncytial or Langhans cells which have been sucked into the circulation at the placental site.

larger and more erectile, and frequently a thin colostrum can be expressed.

Hypertrophy and hyperplasia of the breast affects largely the ducts and lobules, and is caused by the increasing amount of estrogen in the body fluids. The final development of the breasts and the onset of lactation are effects of the hormone of the anterior pituitary—prolactin.

Variation in Secretion. There is great individual variation in the amount of secretion, and the gross size of the breast is no index of the amount of milk available. In decreased or absent secretion (hypogalactia and agalactia), the breast contains few lobules and is

composed largely of fat and connective tissue (Engel). In increased secretion (polygalactia), the lobules are well developed. Persistent lactation (galactorrhea or Chiari-Frommel's disease) is usually associated with atrophy of the uterus and ovaries. The basic cause is unknown (Gilber). Obstruction of the duct of one lobule results in focal cystic dilatation (galactocele).

Acute Mastitis. Acute inflammation of the breasts is rare except during the puerperium. The onset is most frequently in the second and third week. The breast is enlarged, red, and painful. Early, one or a few lobules show the changes of cellulitis. Later, especially if not treated, the entire breast becomes involved, and multiple abscesses form. The bacterial cause in most is the staphylococcus. It enters through fissured nipples improperly cared for.

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LXXI

Diseases Peculiar to the Newborn Infant

The time between the onset of uterine contractions and the completion of the first week of extra-uterine existence probably represents the most hazardous period of life. During the passage through the birth canal the infant is subjected to trauma. Too vigorous effort in manual artificial respiration is occasionally associated with rupture of the liver (Henderson). With the use of machines, excessive positive pressure is the cause of interstitial emphysema and pneumomediastinum (Gumbiner and Cutler). Within a short time

Intra-uterine Age

The pathologist is frequently called on to estimate the age of a fetus which has been aborted or which is found in the uterus at autopsy. The figures of Mall, given in Table 26, are probably the best.

The Premature Infant

The newborn human infant is entirely dependent for existence on the mother. Many

TABLE 26. BASIS FOR ESTIMATING FETAL AGE

Probable Age (Weeks)	Average Crown-Heel Length (Mm.)	Average Crown-Rump Length (Mm.)
4	2½	2½
8	30	25
12	98	68
16	180	121
20	250	167
24	315	210
28	371	245
32	425	284
36	470	316

after birth, respiration must be initiated (Barcroft; Windle and Becker), and the course of the circulation must be adjusted to shunt larger quantities of blood to the lung (Patten). Loss of blood through the placenta even in small amounts may lead to an iron deficiency in the infant (De Marsh, Alt, and Windle). If life is to continue, the digestive processes must furnish nutrition which for nine months has been brought through the placenta. There is little wonder that the mortality in the first year of life is high and that there are diseases peculiar to this period.

of the tissues and physiologic processes are not fully developed even at term. In neonatal deaths of premature infants few pathologic changes are found in the tissues, and it must be concluded that the metabolic processes are not equal to extra-uterine life. In fact, 47 per cent of all neonatal deaths are attributable to prematurity and immaturity, either directly or indirectly.

The survival of a premature infant depends on the size and weight of the child. Under 1000 gm. survival is rare. The survival rate increases thereafter in proportion to weight

with 50 per cent survival at 1500 gm. In infants above 2500 gm. survival is the same as that at term.

Pathologic Anatomy. Aside from prematurity, pathologic changes include petechiae and ecchymoses in all viscera, which in the brain may be a cause of death.

Retrolental Fibroplasia. This lesion is observed in premature infants, especially in those with a birth weight of less than 1500 gm. The essential anatomic change is a persistence of the vasculosa lenta. Both eyes are usually involved. The anterior chamber is shallow. On the posterior surface of the lens there is an opaque vascularized membrane which causes blindness. The cause is unknown (Owens and Owens).

Birth Injuries

Cerebral Birth Injuries. *Pathologic Anatomy.* Injury to the brain is responsible for about 10 per cent of all deaths during the neonatal period. The pathologic findings at autopsy are essentially those of hemorrhage, most frequently in the subdural space. Extradural hemorrhage is rare except in association with fractures. The blood may be either fluid or clotted, and usually spreads as a thin film over the surface of the cerebral or cerebellar hemispheres. Not infrequently there are petechiae throughout the brain, especially in the basal ganglia and in the ependymal tissues. If a child survives for weeks or months, the pathologic evidences of a previous hemorrhage are to be seen in a yellowish brown staining and fibrous thickening of the leptomeninges. In the subdural space, organization is carried out in much the same way that a subdural hematoma is organized, that is, by the ingrowth of the fibrous tissue with giant capillaries from the dura. Occasionally, small focal hemorrhages in the meninges may press on the brain and bring about necrosis or atrophy.

Sources of the Hemorrhage. There are four common sources of hemorrhage: small tentorial vessels coursing along the fibers of the tentorium, the great vein of Galen, cerebral veins near their terminations in the superior longitudinal sinus, the superior longitudinal sinus, transverse sinus, and straight sinus, and the internal cerebral veins.

Causal Factors. Trauma is the outstand-

cause of cerebral birth injury, and results from anything that increases the stress on the fetal head during parturition. The most common agents bringing this about are contracted or malformed pelves, rigid soft parts, precipitate or prolonged labor, abnormal presentation, difficult forceps delivery, breech extraction, and over-large fetal heads. Prematurity is also a factor, since cerebral birth injury is more common in premature than in term infants. In this group, intraventricular hemorrhage is the most common type. Other factors are hemorrhagic disease of the newborn, and probably syphilis.

Clinicopathologic Correlation. The increase of pressure within the cranial cavity causes bulging of the fontanelles and pressure on the medulla, with a consequent slowing of the pulse and respiration and vasomotor collapse. The latter is responsible for the pallid asphyxia of these infants. Since the blood vessel is opened during the birth process, it may take some days for a sufficient amount of hemorrhage to occur to bring about clinical changes. Localizing signs from irritation of the ganglion cells, particularly in the motor areas, produce twitching and convulsions. If there has been any significant damage to the cerebral substance, the result is a false porencephalic cavity, with loss of that part of the brain. If this occurs in the motor area, hemiplegia, monoplegia, or occasionally bilateral hemiplegia results. If the hemorrhage is within the aqueduct of Sylvius or at the base of the brain and becomes organized, so as to occlude the aqueduct or the foramina in the roof of the fourth ventricle, an internal hydrocephalus follows. It is estimated that 2 to 3 per cent of all epilepsy and 1.5 per cent of all mental deficiency has its ultimate basis in cerebral birth injury.

Cerebral Diplegia. In this condition, also known as "Little's disease," the pathologic changes are variable, but the most common lesion is diffuse atrophy of the cerebral cortex, with gliosis of the peripheral gray matter. There is no evidence that it is related to birth injury, but it is probably a defect in the development of the cerebral hemispheres.

Congenital Athetosis. The pathologic lesion here is a loss of ganglion cells in the caudate nucleus and in the putamen and replacement of these areas by myelinated nerve fibers.

Again there is little evidence that the lesion results from cerebral birth injury (Ford).

Injuries to the Spinal Cord. The spinal column is one of the most fragile and the least elastic structures of the fetus, and stress on it during the birth process may result in injury to the column, the meninges, or the spinal cord. Traction by the forceps or a breech delivery is the most common causal factor. Injury to the cord in the high cervical region is incompatible with life, but in the thoracic and lumbar parts it is not lethal, and the children may live for many years with paralysis of the lower extremities (Crothers and Putnam).

Injury to the Brachial Plexus. Difficult labor with traction on the arm may result in paralysis.

Pathologic Anatomy. Pathologic examination of the region of the brachial plexus shows hemorrhage into the tissues about the nerve trunks and tearing of them. Occasionally, the nerves are avulsed from their attachment to the cord. The outer trunk, carrying fibers from the fifth and sixth cervical segments, is most frequently involved. Rarely the phrenic nerve is torn or avulsed.

Clinicopathologic Correlation. The typical picture of lack of innervation through the outer trunk of the brachial plexus is paralysis of the deltoid and spinatus muscles at the shoulder, the biceps, brachialis anticus, and brachioradialis at the elbow, and the extensor at the wrist. The remaining muscles give a characteristic posture and movement. The arm is never raised from the side; it is rotated inward at the shoulder, extended at the elbow, and pronated and supinated at the wrist. This clinical condition is known as "Erb's palsy." Loss of fibers in the inner trunk (eighth cervical and first thoracic) leads to paralysis of the intrinsic muscles of the hands and the long extensors. Rupture of the phrenic nerve results in paralysis of the diaphragm and consequent embarrassment of respiration. If the sympathetic fibers to the head and neck are involved, as they usually are in rupture of the inner trunk, the typical syndrome caused by interruption of the cervical sympathetic chain will be present (Horner's syndrome).

Effects of the Maternal Hormones on the Fetus

Hormones in the blood of the mother are of small molecular size and may cross the pla-

centa to act on the sensitive tissues of the fetus. The most important of these hormones is estrogen.

The testes of the newborn infant are swollen, dark red, and on section bulge from beneath the tunica. Extensive edema and hemorrhage in the interstitial tissue are observed microscopically. There is no significant maturation of the cells of the seminiferous tubules. The ovaries of the newborn infant are large and frequently contain follicular cysts. In the first few months of extra-uterine life, the cysts are obliterated by the growth of fibrous tissue into the cavity.

In the female child the wall of the vagina is thick and the surface thrown into rugae. The epithelium is seen microscopically to be fully keratinized, indicating a maximum estrogenic influence. The uterus is much larger at birth than a few weeks after birth. The endometrium is prominent. In the male infant a histologic study of the prostate shows development of the acini and squamous metaplasia over the verumontanum and in the prostatic utricle.

The breasts in both sexes but more especially in the male are swollen and red. There are hyperemia and hemorrhage into the interstitial tissue, and the epithelial cells are columnar and vacuolated. Not infrequently a small amount of colostrum can be expressed from the nipples.

Atelectasis and Pneumonia in the Newborn Infant

Pathologic Anatomy. In all children who die within a few weeks of birth there may be found parts of the lung in which the tissue is dark red or bluish red and firm. The adjacent lighter pulmonary tissue projects above the firm, depressed foci. On the cut section the architecture of the lung is not discernible. The alveolar walls are thick, and the alveolar spaces are small or entirely absent. The mucosa of the medium-sized and smaller bronchi is irregularly folded, and the blood vessels throughout all parts of the involved lung are dilated and filled with red cells. The cells lining the alveoli may be either cuboidal, as in the fetal lung, or flattened, as in the adult lung. Farber is of the opinion that the former represents a portion of lung which has never expanded, while the latter is lung which at one time was expanded and then collapsed.

These two types of atelectasis in the newborn may be designated "primary" and "secondary" respectively. Certainly, small foci of atelectasis are normal for several days or weeks of life, and atelectasis should be considered the cause of death only when it involves the greater part of both lungs.

Pathogenesis. Careful observations of a number of investigators clearly indicate that there are respiratory movements in the fetus in utero sufficiently strong to cause a tidal flow of amniotic fluid between the lungs and the amniotic sac (Snyder and Rosenfeld).

cerebral hemorrhage and birth trauma, or prematurity.

Pneumonia in the Stillborn and in the Newborn Infant. If there is a tidal flow of amniotic fluid through the lungs a contamination of the amniotic fluid with bacteria may result in pneumonia in the stillborn or newborn infant. In most examples of pneumonia in infants who die within three days of birth, there is abundant evidence of amniotic debris within the bronchioles and alveoli which, together with a history of prolonged labor, early rupture of the amnion, or intrapartum infection

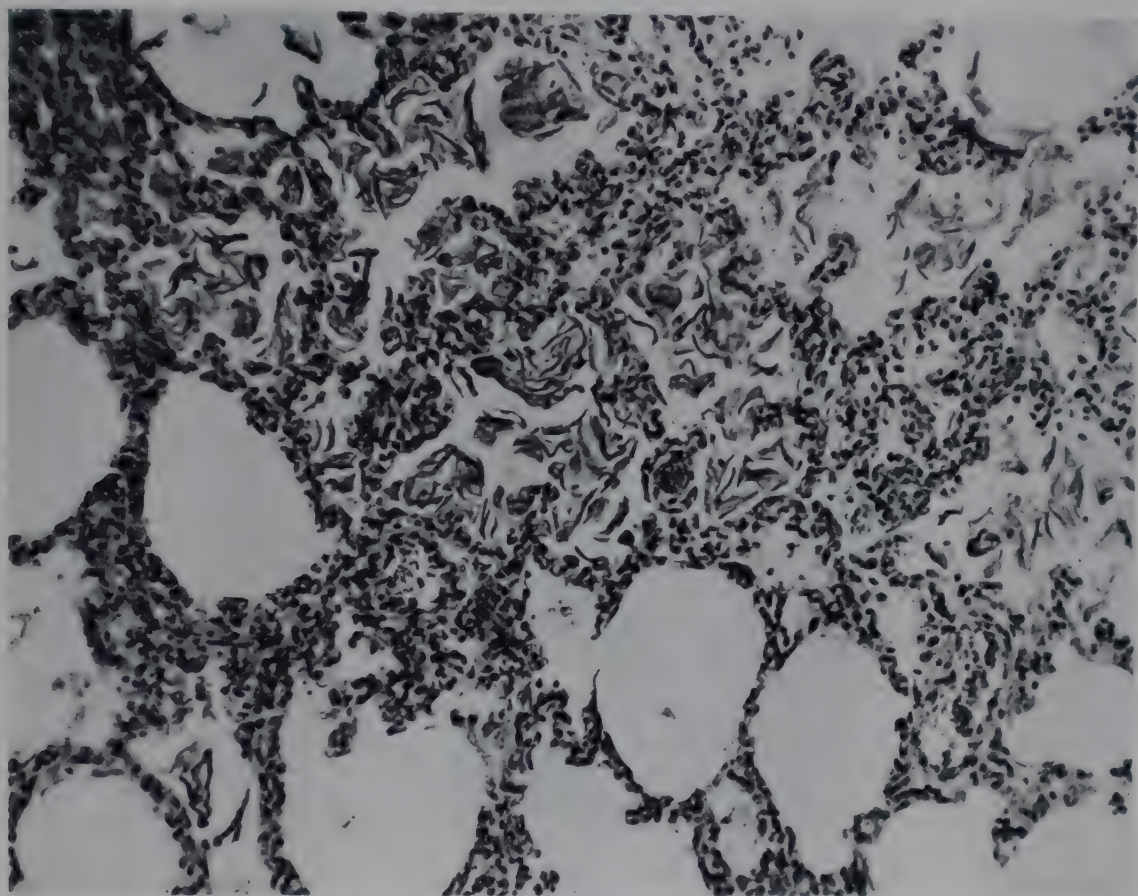


Fig. 289. Squamous epithelium in the pulmonary alveoli of a newborn infant.

Amniotic fluid is also swallowed (Speert). The amniotic fluid which enters the lung necessarily contains desquamated epithelium and other debris. It is possible that this debris occludes the bronchi and is the cause of some of the atelectasis (Paterson and Farr). In addition to this factor, Wilson and Farber have demonstrated three other factors which act to retard an adequate initial expansion of the lung: (1) the cohesion of the bronchial and alveolar walls, (2) an imperfectly developed or injured respiratory center, and (3) an imperfectly developed thoracic musculature. On the basis of experiments in animals it would appear that the first is by far the most important, and that the second and third are important only in special conditions such as

in the mother, makes the above postulation extremely likely. Pneumonia in the newborn is characterized by little fibrin and few leukocytes in relation to the severity of the process.

Hemolytic Disease of the Newborn

In this condition, formerly known as erythroblastosis fetalis, the essential change is the presence in the serum of the infant of Rh antibodies against the Rh-positive cells of the infant. In the more advanced forms of the disease there are pathologic changes in both the placenta and the infant.

Three types of the disease are generally recognized on the basis of associated lesions, i. e., anemia, jaundice, and generalized edema or hydrops.

Pathologic Anatomy. In association with hydrops the placenta is large and frequently weighs over 2000 gm. The ratio of fetal to placental weight is 3:1 or less. The maternal surface is made up of large, pale yellowish gray cotyledons, which are friable. The villi are large, and there is an absence of degenerative changes in the syncytium, with persistence of Langhan's layer. The stroma is

are foci of active erythropoiesis. Similar foci of erythropoiesis may be found in the other viscera (Javert). When there is anemia the bone marrow is aplastic. In other types it is hyperplastic. In metaphyses the zone of provisional calcification may be irregular and poorly calcified. In reticulo-endothelial cells of all organs there is a deposit of hemosiderin, evidence of blood destruction.

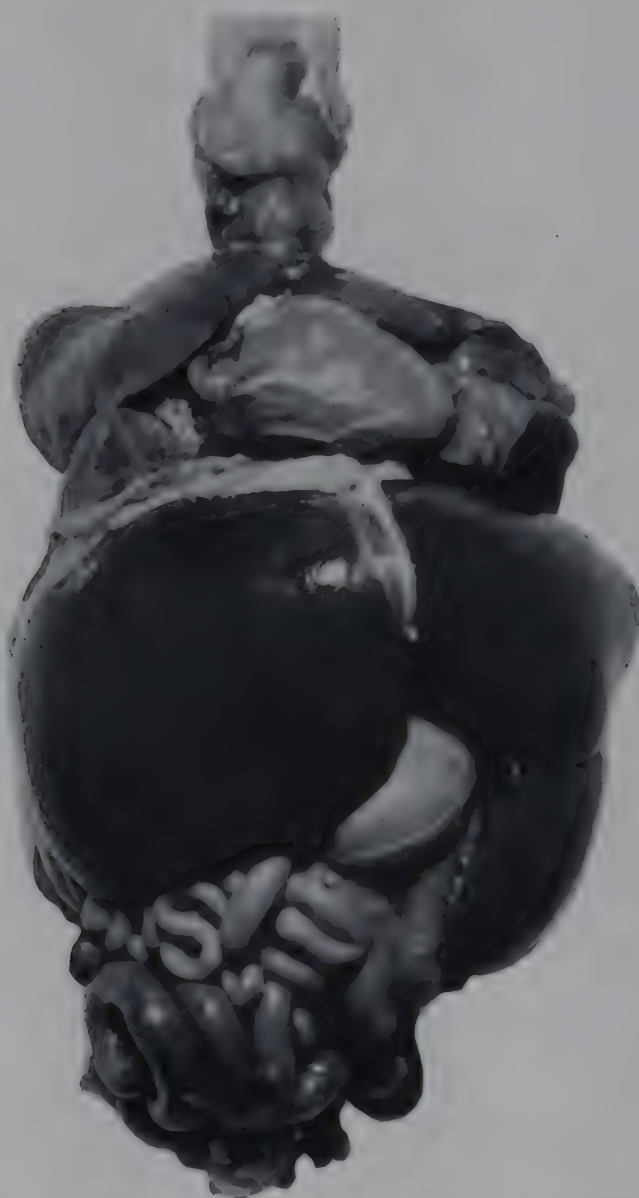


Fig. 290. Organs of an infant with hemolytic disease of the newborn. Note enlargement of the liver and spleen and compression of the thoracic viscera. (Photograph by courtesy of Dr. Sidney Farber.)

edematous, and there are numerous fat-laden Hofbauer cells. The vessels are inconspicuous and there are many areas of intracapillary erythropoiesis (Hellman and Hertig).

In the fetus, external examination may reveal jaundice or edema. The liver is increased in size and grayish yellow. Microscopic examination reveals numerous islands of erythropoietic tissue within the sinusoids. The hepatic cells and the portal canals are normal. The spleen is three to four times normal size. The cut section is grayish red. The malpighian bodies are microscopically inconspicuous, and throughout the red pulp there

In from 5 to 10 per cent of infants with hemolytic disease of the newborn there is yellow pigmentation of nuclear masses of the brain and spinal cords, notably the olives and basal ganglia, known as "kernicterus." The histologic changes are swelling of the ganglion cells, progressing to complete cytolysis, pigmentation of the cells, pigmentation of the interstitial tissue, and the presence of large mononuclear glial phagocytes.

In mild forms of disease pathologic changes are inconspicuous and the diagnosis must be dependent on demonstration of absorbed antibodies.

Pathogenesis of the Cerebral Lesions.

From careful study Zimmerman and Yannet conclude that the pigmentation is secondary to some unexplained primary degeneration of nerve cells. During the period of neonatal jaundice there are few changes in the function of the central nervous system, but in an occasional child with survival there is progressive dysfunction extending over a period of several weeks or months. Similar pigmentation of areas of cerebral softening in adults has been reported (Rutledge and Neubuerger). Such pigmentation has also been observed in jaundice

of the white population and 93 per cent of the colored population of the United States. Differing percentages are observed in other population groups. The factor is inherited as a mendelian dominant. It is estimated that only 5 per cent of Rh negative women ever become immunized. If a woman who is Rh-negative marries a man who is Rh-positive (homozygous), all of the children will be Rh-positive. During intrauterine life some of the fetal red blood cells may escape into the maternal circulation and will there stimulate the formation of anti-Rh substances. These

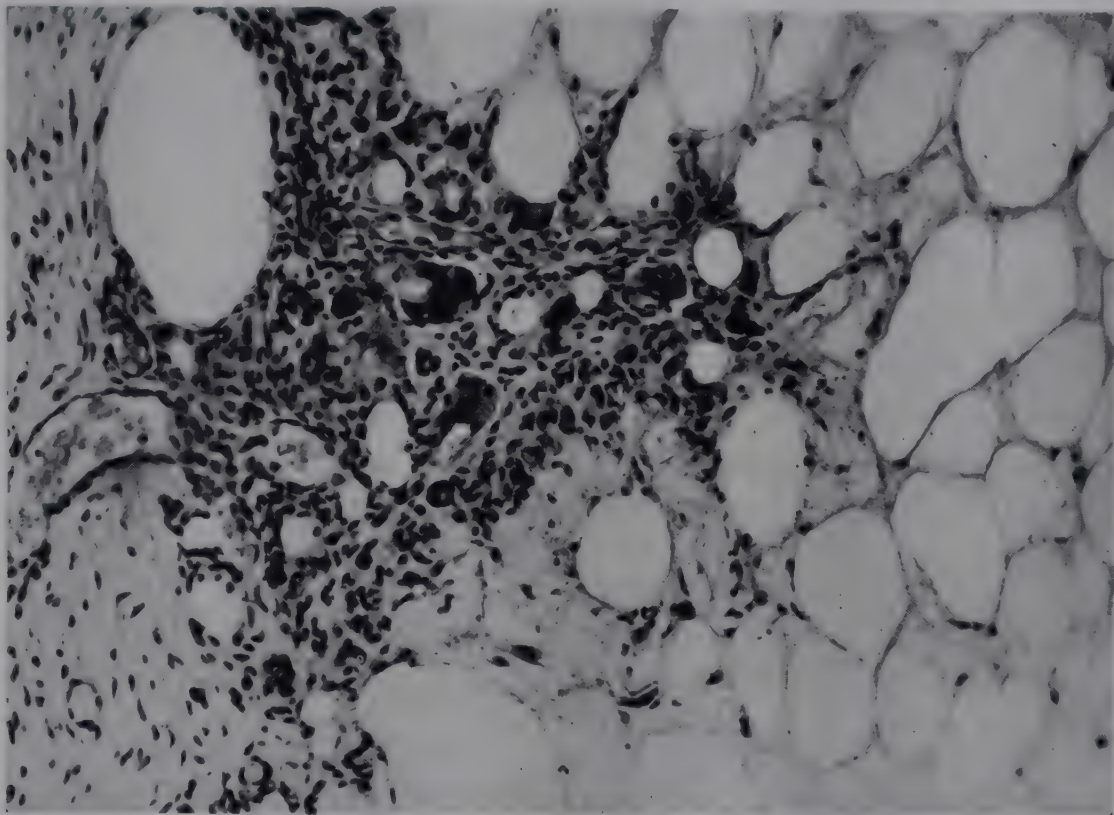


Fig. 291. Subcutaneous fat in sclerema neonatorum. (Tissue by courtesy of Dr. Jacob Furth.)

of infants from other causes, chiefly sepsis and congenital atresia of the bile ducts. Proof that the Rh antibodies are concerned is lacking.

Incidence. Hemolytic disease of the newborn occurs in one of each 250 to 350 deliveries. It is rare in primiparas. Women who have given birth to one erythroblastotic infant are likely to give birth to a second.

Relation of the Rh Factor. It had been noted for many years that often a woman who gave birth to an erythroblastic infant and who was subsequently given a transfusion with her husband's blood had a violent transfusion reaction. From this, Levine and his associates developed a theory concerning the cause of erythroblastosis fetalis. In monkeys there is an antigen attached to the red blood cell known as the "Rh factor" (so named from the word "Rhesus"). It is present in 85 per cent

antibodies, hemolysins, and agglutinins will cross the placenta and destroy the red blood cells of the infant. Similar antibodies may be formed as the result of transfusion with Rh-positive blood; hence a young woman should never be transfused with Rh-incompatible blood.

Subcutaneous Fat Necrosis in the Newborn Infant (Sclerema Neonatorum)

Pathologic Anatomy. Grossly this condition is characterized by the formation in the subcutaneous tissue of irregular, firm masses of fat. The fat cells show necrosis not unlike that of pancreatic fat necrosis and of traumatic fat necrosis. Within the fat cells in frozen sections there are numerous crystals of neutral fats and fatty acids. There are pro-

liferation of the fibrous tissues and slight lymphocytic infiltration. There are numerous giant cells in the areas of fat necrosis. It is generally assumed, but not conclusively demonstrated, that obstetric trauma, acting on the high-melting-point fat of the newborn infant, is responsible for the condition (McIntosh, Waugh, and Ross). The blood lipids are increased (Lazzatti and Hansen).

Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian's Disease). The histologic changes in this condition of adults are similar to those in subcutaneous fat necrosis in the newborn. The lesions occur in nodular form, and the cause is unknown (Johnson and Plice).

Immunity and Disease in the Newborn Infant

It has always been noted that most infants are relatively immune to the usual infectious diseases during the first six to twelve months of life. Investigations show that the newborn calf acquires an immunity through the ingestion of the colostrum, but that in man the immune bodies cross the placenta and are not contained in the colostrum. Correlated studies of the structure of the placenta have given a satisfactory rationalization of these two opposing results: in the pig and cow the number of layers of tissue between the maternal and fetal blood is excessive, and it is reasonable to believe that larger molecules cannot cross. On the other hand in man and in the rabbit there are only two layers of cells (Mossman). The immune bodies do not pass into the fetal circulation until about the fifth month, when the syncytial layer of the chorion undergoes degeneration (Flexner and Gellhorn). Vaccination of the mother in the last trimester of pregnancy confers immunity on the newborn infant (Cohen and Scadron). Studies of the permeability of the placenta with radioactive compounds such as sodium should yield valuable information (Gellhorn, Flexner, and Hellman). The remarkable phenomenon that the fetus in utero is susceptible to certain viral diseases until about eighteen hours before birth, when resistance suddenly develops, is at the present time unexplained (Dettwiler, Hudson, and Woolpert).

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LXXII

Teratology

Teratology is that division of biology or medicine concerned with the study of monsters, or terata. Superficially, it is easy to recognize monsters, but when the details are examined the transition from constitutional differences through trivial congenital anomalies to actual terata becomes less distinct.

Historical. Monsters have always been of great interest, and primitive man sought for some explanation in the supernatural. The Chaldeans believed that the birth of a monster was related to the astral combination at that time. Among polytheistic peoples many of the gods were in the form of monsters. The Greek god Polyphemus was a cyclops. A siren was a sympodial fetus. A centaur was an infant with two pairs of lower extremities. Throughout the medieval ages and up until almost modern times, the theory of maternal impressions was popular. Some mental experience of the pregnant woman was believed to have been impressed on the developing fetus. A speckled child was thought to be so marked because the mother had during pregnancy gazed long and earnestly at some pebbled stones (an instance of multiple congenital nevi). Gradually in the last century these fanciful ideas have given way to theories based on observation and experimental study.

Modern Theories of Causation. Logic dictates that an anomaly may result from defective or exhausted germ plasma, or from injury of the growing embryo. The significance of the former is illustrated by the observation that terata are more common in the higher birth ranks (fifth to the fifteenth child) than the expectancy in all children (Murphy and Mazer). In some types of anomalies heredity is apparently a factor. Injury to the fetus in utero may be of many types: traumatic injury to the abdomen short of destruction of the fetus, defects of implantation, diseases of the

chorion or amnion that interfere with nutrition, changes in the chemical composition of the fluids in and about the fetus, and thermal alterations. It is also probable that bacterial toxins in the blood of the mother and therapeutic drugs influence the growth of the fetus.

Relation to Infectious Diseases. If a pregnant woman has rubella (German measles) during the first trimester of pregnancy, the likelihood of some anomaly, especially of the heart, in the fetus is high. Other infectious diseases may have a similar influence but it is less apparent (Aycock and Ingalls).

Experimental Teratology. Many of the before-mentioned theories of causation are based on experimental observations. The influence of chemical agents has been extensively studied. If sea urchins' eggs or frogs' eggs are placed in a solution of lithium salts, the layers of the blastoderm invert in development. In *Fundulus* strong lithium salts will cause failure of development of the eyes and other defects (Stockard). Anomalies of the genital tract may be produced by a disturbance in the ratio of androgens to estrogens in the pregnant rat. For example, the injection of a slow-acting estrogen during the last half of pregnancy in the white rat results in pseudo-hermaphroditism of the male fetuses (Greene, Burrill, and Ivy). Recently it has been shown that dietary alterations in pregnant animals may induce anomalies of the fetuses (Nutrition Reviews). Finally, it has been shown that cooling of the eggs of chickens during critical stages of development brings about anomalies of single organs or of the entire organism.

Frequency. For every 100,000 conceptions there are 7000 pathologic embryos and 615 monsters. About one-third of all these, or 2 per cent of all conceptions, are well-formed monsters. Of each 100 monsters, 75

are aborted in the early months of pregnancy, and 25 go on to term. On this basis it is estimated that about 0.6 per cent of all births at term result in terata of major proportions (Mall).

Classification. The most satisfactory working classification of the terata is that of Bal-lantyne:

affect only one organ system, and are best discussed in the chapters devoted to each system. The pantosomatous and heterotopic types involve the greater part of the body and will be described here.

Pantosomatous Terata. Abnormal smallness of all parts of the body symmetrically and proportionately is *microsomia*, or true dwarf-



Fig. 292. Anencephalic monster. Note defect in skull and prominent supraorbital ridges.

TERATA

(*Monstrosities and Anomalies*)

- A. Monosomatous (a single individual involved)
 - I. Pantosomatous (the anomaly affects the whole or nearly the whole body)
 - II. Merosomatous (the anomaly affects only a part of the body)
 - III. Heterotopic (the anomaly affects only the arrangement of the parts of the body)
- B. Polysomatous (two or more individuals involved)
 - I. Twins, entirely separate but with a single chorion
 - II. Twins, united by their umbilical vessels
 - III. Twins, united more or less completely (double monsters)
 - (a) Symmetrically united
 - (b) Asymmetrically united
 - IV. Triplets, quadruplets, and quintuplets

Monosomatous Terata

In monosomatous terata a single individual is involved. The merosomatous types

ism. It should be sharply separated from dwarfism resulting from local defects such as chondrodysplasia. *Macrosomia* is the converse. The cause of these two conditions is probably to be found in the endocrine glands, particularly the pituitary. Fetal macrosomia when the mother is diabetic is well known. Unilateral macrosomia or *hemihypertrophy* is more difficult of explanation. In the fully developed condition, one side of the body, more frequently the right, is larger than the other side. Minor grades are seen, such as a large thumb or foot. Crossed hemihypertrophy (one arm and the opposite leg) has been observed. An association with nevi and telangiectasis has been noted, and the enlarged parts are more liable to infection. The converse condition, unilateral microsomia or *hemiatrophy*, is also known.

Heterotopic Terata. This term includes

states in which the viscera are partially or completely transposed (*situs inversus*). In early embryonic life the thoracic and abdominal viscera are symmetrically disposed about the midline. Normally there is a rotation and growth to the right, while in *situs inversus* the twist is to the left. Partial transposition may involve the abdominal and thoracic organs, only the thoracic organs, or only the abdominal organs (Mayo and Rice). Dextrocardia, or transposition of the heart, is frequently associated with other anomalies of this organ. It is of practical importance to know that the peripheral pain-bearing pathways may not be transposed, so that the somatic localization of visceral pain may be normal in a patient with *situs inversus* and appendicitis, cholecystitis, or angina (King). The association of transportation of the lungs with bronchiectasis is a well recognized condition.

Polysomatous Terata—Multiple Pregnancy

Monochorionic twins represent the simplest type of polysomatous terata. About 20 per cent of all twins are uniovular or identical. The incidence of multiple pregnancies is as follows:

	Once In:
Twins	85.2 births
Triplets	7,628 births
Quadruplets	670,734 births
Quintuplets	41,600,000 births
Septuplets	4 authentic records
Sextuplets	3 authentic records

There is no evidence of a hereditary factor in monozygotic twins, but it is definite in dizygotic twins. The factor is carried by both the father and the mother (Greulich).

Allantoido-angiopagus Terata. This category of placental parasites includes the rudimentary fetuses which are attached to the co-twin by the umbilical vessels. The rudimentary twin may be amorphous, may lack a head, may consist of only a head, or may possess no heart. The co-twin ordinarily shows no malformations.

Double Monsters. It is not possible here to discuss all the types of double monsters, or united twins. If the incomplete separation is

from the head caudalward the monster is termed “anadidymous”; if from the legs cephalad, “katadidymous”; and if both from above and below, “kata-amadidymous.” When the fission is almost complete, the name depends on the site of union: “sternopagus,” “xiphopagus,” “pygopagus,” and “craniopagus.” In the category of double monsters are also included the parasitic twins in which a rudimentary fetus is attached to some part of the body: “cephaloparasitic,” “thoracoparasitic,” etc.

From the clinical standpoint monsters are of importance because of the difficulty in delivery. An embryotomy or a cesarean section may be necessary to empty the uterus. A radiograph during the ninth month of gestation frequently permits of an early diagnosis.

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LXXIII

Heredity and Constitution in Relation to Disease

To assume that human disease begins at birth would lead to a lack of knowledge concerning some of the most interesting and important diseases. It is well known that children may be born with evidence of active or healed infectious diseases, such as active smallpox. Such diseases may be classified as congenital diseases, and should be sharply separated from congenital anomalies and from hereditary diseases. A congenital anomaly is a failure or a defect in the embryologic development of an organ or structure. A hereditary disease is one which appears in accordance with the mendelian law of heredity.

Hereditary Disease

During the development of the egg and of the sperm within the respective gonads, the final cell division is one of reduction of the number of chromosomes within the cell. This involves an equal division of the pairs of genes within each chromosome. With fertilization of the egg by the sperm the characteristic total number of chromosomes is restored and each gene is paired against another gene, known as its "allelomorph." One member of this pair is maternal and the other paternal. For example, the maternal gene for eye color may indicate brown while the paternal gene is for blue. From experience it is known that the brown is dominant and that the offspring will be a hybrid, carrying in the sex cells brown and blue, but having brown eyes.

Sex-Linked Characters. In a few instances a gene determining some physical characteristic or the presence of a disease is carried in the same chromosome that determines sex. All of these diseases, designated as "sex-linked," are recessive, and therefore are carried by one sex and appear as pathologic conditions in the other sex. The best known

example is hemophilia. Women never suffer from the condition (unless both parents are hemophilic—a remote possibility), but their sons rarely escape it. Color blindness is inherited in a similar way.

Familial Disease. Many observations have been made on diseases which occur in families, with no clear evidence of inheritance according to the mendelian principles. So-called "familial disease," however, is nothing more than an inherited disease recessive in character and therefore only appearing under unusual conditions.

Variation in Types of Inheritance. In some families a disease may be dominant, and in other families recessive. For example, peroneal muscular atrophy appeared as a sex-linked, recessive characteristic in four generations of one family, while it was a non-sex-linked dominant characteristic in another family. This probably means simply that there are several pathologic conditions that can lead to peroneal muscular atrophy. One of these is a sex-linked recessive, the other a non-sex-linked dominant.

Evaluation and Study of Hereditary Diseases in Man. There are a number of approaches to the demonstration that a disease is hereditary in man (Macklin). If it is assumed, probably correctly, that man carries a number of undesirable recessive characteristics, it follows that these would be more common in the children of consanguineous marriages than in the usual type of human relation. The average number of consanguineous marriages in the Caucasian race is 0.2 per cent. In the records of 131 families with one or more amaurotic idiots, there were 13 families, or 10 per cent, in which the parents were cousins. A further line of evidence, and a particularly important one, is the presence of the same disease in identical twins. Accord-

ing to the laws of pure chance, given 100 pairs of twins, 37.5 per cent of them should be of unlike sex, and 25 per cent of them should be identical twins. In one group of 14 sets of diabetic twins, there was only one pair, or 7 per cent, of unlike sex, and 10 pairs, or 71 per cent, were said to be identical twins. Both of these figures differ from the expected, and it therefore follows that some diabetes is inherited.

A third method of procedure is the study of all members of a given family, with the demonstration that a disease is commoner in this family than in the population at large, and that it follows some of the known laws of genetics. The related and unrelated members of a family may be investigated. Tuberculosis has been found to be commoner in children of tuberculous parents than in the population at large, but it has also been found to be just as common in the husbands and wives of tuberculous mates as in the children. The condition is manifestly not inherited. In a study of Friedreich's ataxia in 117 families, there were no examples of the disease in both husband and wife. In 32 families one parent and one or more children were diseased, and in 85 families the children only had the condition. It is apparent that neither infection nor environment is a causal agent and that the hereditary factor is probably recessive.

Constitution and Disease

Long before scientific medicine evolved, physicians recognized that certain types of persons frequently suffered from certain diseases. For example, the heavy-set, florid person is apt to die of apoplexy; the long, thin person to suffer from dyspepsia and nervousness; and the person with a flat chest and sunken cheeks to have tuberculosis. It is the problem of the physician to separate cause from effect and to evaluate accurately the factors entering into this apparent constitution. He must also answer the questions whether this difference is genetic or developmental in origin or both, and whether it is due to differing degrees of an acquired reaction on the part of persons who have been subjected to some definite and peculiar environmental stress or strain. He must further recognize that constitution is not a static or fixed affair, but a developmental condition depending on

the genetic composition of the individual to a large extent, but also in a most important degree on the manner of development and growth. Thus a person's constitution during childhood might be very different from his constitution at twenty or fifty or seventy years of age.

The Elements of Constitution. The physical or anatomic constitution can be determined by the usual methods of physical examination or anthropologic measurement. There are many other elements in constitution however, notably physiologic, psychologic, and immunologic. Not all persons metabolize or store a given amount of glucose in the same way, nor do they produce antibodies against a bacterium with equal facility.

Factors Determining Constitution. *Racial, Familial, and Somatic Factors.* Every organism, whether man or animal, is a composite of racial, familial, and individual characteristics. The physical differences in the races are evident, and they form the basis of the recognition of a white, yellow, red, and black race. The incidence of many diseases is the same in all of these races, while the incidence of others shows great variation.

The factor of family is concerned not only with one's immediate family but also with the family in a broader sense. The Jewish people for many centuries have closely intermarried, and they represent not a race but a large family. It is said that some diseases, such as polycythemia vera and thrombo-angiitis obliterans, are more common in Jewish people than in other members of the white race. In all evaluations of this sort one must of course consider habits and environment, since they also differ.

The factor of a somatic mutation also enters into the constitution of any one person. At any time in the biologic evolution of a species, individuals may be born with characters different from those of all of their ancestors. In experimental animals this occurs both spontaneously and following definite experimental procedures. Thus the administration of a small dose of x-rays to certain strains of mice may lead to the appearance of many newborn mice without kidneys, or with internal hydrocephalus. These families breed true, and it must be assumed that there is a permanent mutation in the germ plasma, in contrast to a congenital anomaly, in which a single individual, and

not all of his descendants, has this characteristic.

Factors Concerned with Development and Changes Dependent on Environment. These comprise the second great group. During intra-uterine development a period of slowing of growth, or some injury preventing growth in a local area, will influence the constitution of the resulting individual. The same is true of extra-uterine life. Persons who live near the seacoast are likely to be different from those who live at a distance from the sea. This is probably related to the amount of available iodine and the stimulation for growth received from an active or from an inactive thyroid gland.

Factors Dependent at Times on Genetic Composition and at Times on Environment. The best example of this group is the endocrine system. It has been noted above that individuals living for generations along the sea are more active, taller, thinner, and have a better developed thyroid. An animal organism can also inherit the structure of the thyroid. This is well shown in the various breeds of dogs, where the small terrier types have an active thyroid in contrast with the heavier, slower more amiable breeds where the thyroid is inactive. Localized defects of growth may also be inherited, as is shown by the legs of the dachshund (Stockard).

Thus the ultimate physical make-up of a person depends on the inheritance of many factors, mutations, and the rate of growth of the body as a whole and of each part.

Relation of Constitution to Disease. As noted in the introduction to this section, the occurrence of disease in certain physical types was recognized by the early Greek physicians. Draper of Columbia University in New York has been the modern proponent of this theory. From certain anthropologic measurements he has established certain types, and finds that they are related to definite diseases. For example, he finds that most persons with peptic ulcer are tall and thin, and nervous, while most persons with disease of the gallbladder are more rotund, and are likely to be inactive both physically and mentally. There are great opportunities for investigation in this field, and in the future more precise statements can be made on the basis not only of anatomic but also of physiologic, psychologic, and immunologic reactions.

The Effect of Race on the Incidence of Disease

Most observations which have been made on the relation of race to disease involve many factors other than racial constitution. For example, the people of India suffer from plague and leishmaniasis not because of any constitutional difference, but because they happen to live in an area where these diseases are endemic, and under hygienic conditions which predispose to the perpetuation of the disease. The people of South China suffer frequently from calculi in the urinary bladder, not because of race, but because of the nature of the water and the diet. Men in China show a high incidence of carcinoma of the penis, while in Jewish men this form of cancer is almost unknown. The explanation is found in the universal practice of circumcision at birth in the Jewish people, and the almost universal lack of circumcision among the Chinese. Many other examples could be cited, and the greatest care is necessary in the evaluation of this problem. There are, however, a few definite differences.

Carcinoma. Carcinoma of the prostate in the Chinese is an extremely rare disease, and so far as is known this cannot be explained on any basis other than that of a racial constitutional difference. Carcinoma of the cervix among Chinese women constitutes about 30 per cent of all tumors. This may be caused by a lack of hygiene of the vagina, but it seems possible that there is also a factor of a difference in the basic endocrine status of the Chinese and Caucasian woman.

Inherited Disease-Producing and Lethal Genes. It is said that the sickle cell trait is not found in any race other than the Negro, and that when it is found in an apparent Caucasian it indicates a mixture of Negro blood. In contrast to this, certain conditions such as primary muscular atrophy, seen in Caucasians, are extremely rare in the Negro. The blood groups are directly inherited, as a series of three multiple allelomorphs, A, B, and O, of which A and B are dominant and O is recessive. So far as is known there is no connection between the blood group of a person and resistance or susceptibility to disease.

Resistance and Susceptibility to Bacterial Infections. Bacterial diseases are so dependent on hygienic conditions, the presence of insect

vectors, and many other factors, that it is difficult to evaluate accurately an increased susceptibility or resistance to a specific disease. Thus Negroes in general are far more promiscuous in their sexual relations, and the general incidence of syphilis is much higher than in Caucasians—about 20 per cent of all Negroes have a positive Wassermann reaction. On the other hand, this cannot explain the fact that the Negro, when he develops syphilis, shows a much greater incidence of syphilis of the cardiovascular system, and a much lower incidence of syphilis of the central nervous system, than white persons in the same country. It must be assumed that there is some basic racial difference in the reaction to syphilis. In the same way the Negro lives under general hygienic conditions that predispose to massive infection with tubercle bacilli. Yet there have been repeated studies which indicate that the same dose of tubercle bacilli will produce more severe disease in the Negro than in the white man. Although other factors cannot be eliminated, it would appear that the Negro is less resistant to tuberculosis, probably because of a shorter exposure over the centuries. The first slave was introduced into the North American continent in 1619. The Caucasian in Europe has been exposed to tuberculosis for more than three thousand years, while the Negro has been exposed for only three hundred years (Lewis).

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LXXIV

Diseases Peculiar to the Aged—Gerontology

With the discovery of better methods for the prevention and treatment of the infectious diseases, life expectancy has been increased and correspondingly the percentage of older individuals in the population is greater.

In the United States the life expectancy at birth of a white male child in 1901 was 48.23 years and in 1939 was 62.60 years, a gain of 13.37. On the other hand the life expectancy of a man at age 60 in 1901 was 14.35 years and in 1939 was 14.36 years, a gain of 0.01 year or 3 days. It is clear that much has been accomplished for the younger person but little or nothing for the older individual. This indicates that medicine and medical research must increasingly give attention to the processes of aging and the diseases of older persons.

In 1850 only 2.6 per cent of the population were over 65 years of age. By 1900 there were 4.1 per cent and by 1940 6.8 per cent. With present mortality rates those over 65 years in 1980 will constitute 14.4 per cent of the population of the United States. This increase of the older segment of the people presents problems not only to medicine, but also to those interested in social relations, housing, hospital facilities, economic stability, and many other fields.

It is impossible in a single chapter of a general textbook to give a complete review of aging and diseases of the aged. Hence, the discussion will be limited to the generalities of the anatomic and physiologic changes with age.

Anatomic Changes with Age

The basic anatomic changes with age are two: parenchymal atrophy and relative increase of interstitial tissue, and accumulation and infiltrations with foreign substances.

Parenchymal Atrophy. Parenchymal at-

rophy may be reflected in the size of entire organs, in the number of cells or units in an organ, and in the size of each cell. The weight and size of all organs decrease with increasing age. Some organs exhibit this change to a greater extent than others: e. g., liver, spleen, and primary and secondary sexual organs. As in starvation, certain organs are only slightly altered: e. g., brain and heart. There is decrease in size as the result of a combination of the other two changes—decrease in number of cells or units and in size of each cell or unit.

In the kidney there is a decrease in number of glomeruli, independent of disease, both in man and in rats (Moore). The heart shows a decrease in number of fibers (Karsner, Saphir, and Todd). The number of nerve cells in the brain and ganglia becomes less with increasing age.

The characteristic cell of the older organism is small with a dense cytoplasm and a small, deformed, highly chromatic nucleus. This cell is typified by the heart muscle fiber in atrophy.

Although fat tissue and elastic fibers are not usually considered as parenchymal elements, they show atrophy with increasing age. There is a disappearance of the subcutaneous fat and of the fat depots. The loss of the elastic fibers of the subcutaneous tissue is responsible for the loose appearance of the skin. In the lung, the decrease in elastica is related to the development of senile or small lung emphysema.

The atrophy of parenchymal elements of necessity make the interstitial tissue more prominent. It is doubtful that there is any actual proliferation of connective tissue as an essential part of the aging process.

Infiltration of Foreign Substances. The accumulation and infiltration of foreign ma-

terial is observed in various forms. In many cells, notably nerve cells, myocardial fibers, and liver cells, a light brown pigment accumulates and is responsible for the brown color of these organs in older people. Both chemical and histologic studies show a progressive increase in calcium in the tissues with age. In arteries, especially the aorta, the calcium is deposited as an incrustation on the elastic fibers of the media. In some places such as the pancreas, the loss of parenchyma may be made up in part by infiltration with fat tissue.

Physiologic Changes with Age

The basic physiologic change with increasing age is an inability of the physiologic processes to adapt to stress and strain as quickly and as fully as at younger ages. This phenomenon is seen in the fact that the older person is less able to withstand a cold or hot environment and exercise. With exercise the heart rate and minute volume output do not increase as quickly and return to normal more slowly. The kidneys do not adjust as rapidly as in the younger person to a disturbance in the acid-base balance, nor do they restore it to normal as rapidly.

Associated with this instability of the homeostatic mechanisms there is actual decrease of some physiologic functions, possibly related to anatomic atrophy. For example, there is a decrease in the amount of gastric juice secreted and of the activity of pepsin and hydrochloric acid.

The Causes of the Aging Process

Many theories have been advanced to explain the anatomic and physiologic changes which occur with increasing age. None is satisfactory. There are three basic theories worthy of consideration: endocrine, nervous, and arterial.

The endocrine theory postulates that decrease in hormonal stimulation, especially from the thyroid and gonads, is basic to all other change. Those who are impressed with the atrophy of nerve cells explain the other alterations on the basis of a lack of nervous stimulation.

There can be little doubt that arterial change with decreased minute volume flow through a part plays an important role in producing some of the changes of age.

The fallacy of all these three theories is that one change is selected as the cause of the others, without explanation of why the primary alteration occurred.

Progeria

Progeria is a peculiar condition of children in which there is a combination of appearances of immaturity and senility. Signs usually appear at about one year of age in a previously normal infant. Outstanding changes are dwarfism, loss of hair and subcutaneous fat, and development of arteriosclerosis.

Anatomic changes are nonrevealing in terms of cause and pathogenesis. The arteriosclerosis is of the same type as seen in adults. The sclerosis of the coronary arteries may lead to occlusion and formation of a cardiac infarct.

Physiologic studies suggest a basic defect of metabolism in which there is excessive utilization of calories for energy. This indicates there are not available calories for growth (Talbot, Butler, Pratt, MacLachlan, and Tannheimer).

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PART VII

DISEASES OF UNKNOWN OR OBSCURE
CAUSE—SYSTEMIC PATHOLOGY

Causes and Effects of Obstruction of Hollow Viscera

In the first six parts diseases with a known causal agent have been discussed. There remain an unfortunately large number of diseases and pathologic lesions the cause of which is unknown. Many of these diseases bring about obstruction of the hollow viscera.

In general, obstruction of a hollow viscus may be caused by one of four types of lesion: paralysis of the muscle, the presence in the lumen of a foreign body, a lesion in the wall of the viscus which grows into and occludes the lumen, and a lesion in an adjacent organ or structure which presses upon the hollow viscus.

Paralysis of the Musculature of a Hollow Viscus. Fluid in the gastro-intestinal tract, in the urinary tract, and in the ducts of all of the hollow organs is propelled forward by peristaltic waves which pass along the viscus. If there is paralysis of the musculature of a part of the intestine, the peristaltic wave cannot propagate itself over this segment, and obstruction and dilatation of the intestine result, a condition known as "paralytic ileus." It occurs in association with acute inflammations of the peritoneum and is a troublesome postoperative complication in some patients after laparotomy. Temporary paralysis probably also plays a part in dilatation of the urinary tract in association with infection. Some instances of acute dilatation of the stomach appear to result from overeating. Similarly, continued distention of the bladder depresses the stimulation for micturition, and there may even be difficulty in starting the urinary stream.

Foreign Bodies in the Lumen of a Hollow Viscus. Foreign bodies, in general, may be classified as exogenous or endogenous. Examples of *exogenous foreign bodies* are the peanuts, tacks, safety pins, and buttons found in the respiratory and alimentary tracts

of children. Exogenous foreign bodies are occasionally found in the rectum and in the urinary tract. Occasionally, an exogenous foreign body such as a bullet is introduced into the lumen of one of the deeper hollow viscera. *Endogenous foreign bodies* represent those formed within the body, either from normal constituents of the body or from artificially introduced material. A small foreign body introduced into the urinary bladder is soon covered by a deposit of urinary salts and is built into a structure many times the size of the original body. The commonest endogenous foreign bodies are calculi formed within the ducts of the secretory glands of the body. The most important of these are stones in the biliary tract, a condition known as "cholelithiasis." Of almost equal importance are calculi in the urinary tract, either in the renal pelvis, in the ureter, or in the bladder. Less commonly, concrements are formed in the pancreatic ducts, in the salivary ducts, and in the prostate. The calculi in the duct of a gland should not be confused with calcified thrombi in veins, known as "phleboliths."

Lesions in the Wall of a Hollow Viscus. A mass of tissue growing in the wall of a hollow viscus may project either into or away from the lumen. In the stomach the contrast between these two types of lesions is striking. The carcinoma of the stomach grows as a mass into the lumen and brings about obstruction. The sarcoma of the stomach, in most instances, grows toward the peritoneal cavity and does not bring about any serious occlusion of the stomach. This difference between carcinoma and sarcoma applies to the entire gastro-intestinal tract. The most important of the lesions in the wall of a hollow viscus which bring about obstruction are tumors; and in the succeeding chapters major emphasis will be given to them. In the smaller hollow

viscera, such as the nose and the ducts of the glands, inflammation of the mucosa, as in the common cold, may produce sufficient swelling to occlude the lumen. Edema and swelling of the ampulla of Vater may be the cause of obstructive jaundice in an occasional patient.

Extrinsic Lesions. Most of the hollow viscera are capable of considerable displacement without serious interference with their physiologic activity. Thus a ureter may be pressed aside by a small tumor; but if the tumor is 20 cm. in diameter, the pathway taken by the ureter to go around the tumor will be so long that the lumen will become decreased in diameter. Inflammations and tumors which invade tissues diffusely may press upon a hollow viscus from all sides, and occlude the lumen. Examples of this are frequently seen about the ureter and about the common bile duct.

Secondary Effects of Obstruction of Hollow Viscera

Dilatation. As all of the hollow viscera except the respiratory tract are filled with fluid, the first immediate effect of obstruction is the accumulation of fluid above the obstruction, and dilatation of the hollow viscus.

If the obstruction occurs in the *upper gastro-intestinal tract*, the patient instinctively stops further ingestion of fluids and solids which would increase the dilatation. The fluids which are already present and those which accumulate from secretion are in part removed by emesis.

In those viscera such as the *urinary tract* and the *biliary tract*, where there is no connection with the exterior of the body above the obstruction, other methods must be depended upon to prevent extreme accumulations of fluid. Each kidney secretes about 750 cc. of urine a day. It is apparent that following complete obstruction of a ureter the renal pelvis would fill the abdomen within a few days. As the renal pelvis dilates, it comes in contact with the larger renal veins, and there is resorption of the fluid into the venous blood, a process known as "pyelovenous back-flow." There is probably also some diminution in the secretion of urine. The force responsible for the secretion of urine is the difference in the blood pressure and the osmotic pressure of the plasma. The pressure

in the renal pelvis and in the renal tubules could reach a point exceeding this difference, and thus stop the secretion of urine.

In the biliary tract this stoppage of secretion is of considerable importance. An occlusion of the hepatic duct will lead to the accumulation of a clear, slightly viscid, colorless fluid in the dilated bile ducts, known as "white bile." The explanation is that the liver is unable to secrete against pressure, but the mucosal cells of the bile ducts can secrete against pressure. Following the complete obstruction, there is resorption of the contained bile and no further secretion of bile, but mucus collects within the lumen and brings about dilatation of the ducts. On the other hand, obstruction of the common bile duct leads to the accumulation of a dark, thick fluid in the entire biliary tract and in the gallbladder. It is assumed that the gallbladder resorbs a sufficient amount of water to relieve the pressure and allow the liver to continue to secrete.

Dilatation of the *ventricles of the brain* presses the brain against the solid, bony calvarium. In contrast with other organs, where the entire organ can increase in size and thus minimize atrophy of parenchyma, increasing dilatation of the ventricles occurs only with increasing atrophy of cerebral substance.

Secondary Effects on the Secretory Structures. In general, occlusion of the ducts of a secretory organ leads to atrophy of the secretory cells of that organ. Dilatation of the renal pelvis, known as "hydronephrosis," presses upon the substance of the kidney and brings about progressive atrophy. There are fibrosis of the interstitial tissue, loss of renal tubules, and obliteration of glomeruli. Obstruction of the pancreatic duct eventually leads to complete atrophy and disappearance of the acinic tissue. There remains a mass of fibrous tissue, in which are embedded the islands of Langerhans (Fig. 293). Obstruction of the biliary tract leads to fibrosis and proliferation of the bile ducts throughout the liver, a condition called "constructive biliary cirrhosis."

Hypertrophy. In any hollow viscus with an adequate muscularis, obstruction immediately leads to hyperactivity of the muscle above the obstruction. This hyperperistalsis is largely responsible for the pain which is an outstanding and compelling symptom in ob-

structions of hollow viscera. Continued increased work on the part of the muscle leads to hypertrophy. In carcinoma of the colon when the obstruction has endured for many months, there is conspicuous hypertrophy of the muscularis above the lesion. In the bile ducts where the muscle is sparse there is little evidence of hypertrophy. In an obstruction caused by a small tumor mass projecting into the lumen of a hollow viscus, hyperperistalsis, in an attempt to push the mass onward, leads to pedunculation. Polyps of the intestine and

bacteria can enter the tissues of the wall. Decubital ulcers formed in the appendix by fecaliths are probably an important causal factor in acute appendicitis. Decubital ulcers in the biliary tract are responsible for the fistulas between the gallbladder and common bile duct and the gastro-intestinal tract.

Recovery from Dilatation. In an organ with abundant musculature and adequate amounts of elastic tissue, dilatation is reversible, and when the obstruction is removed the viscus returns to a normal size. In structures with

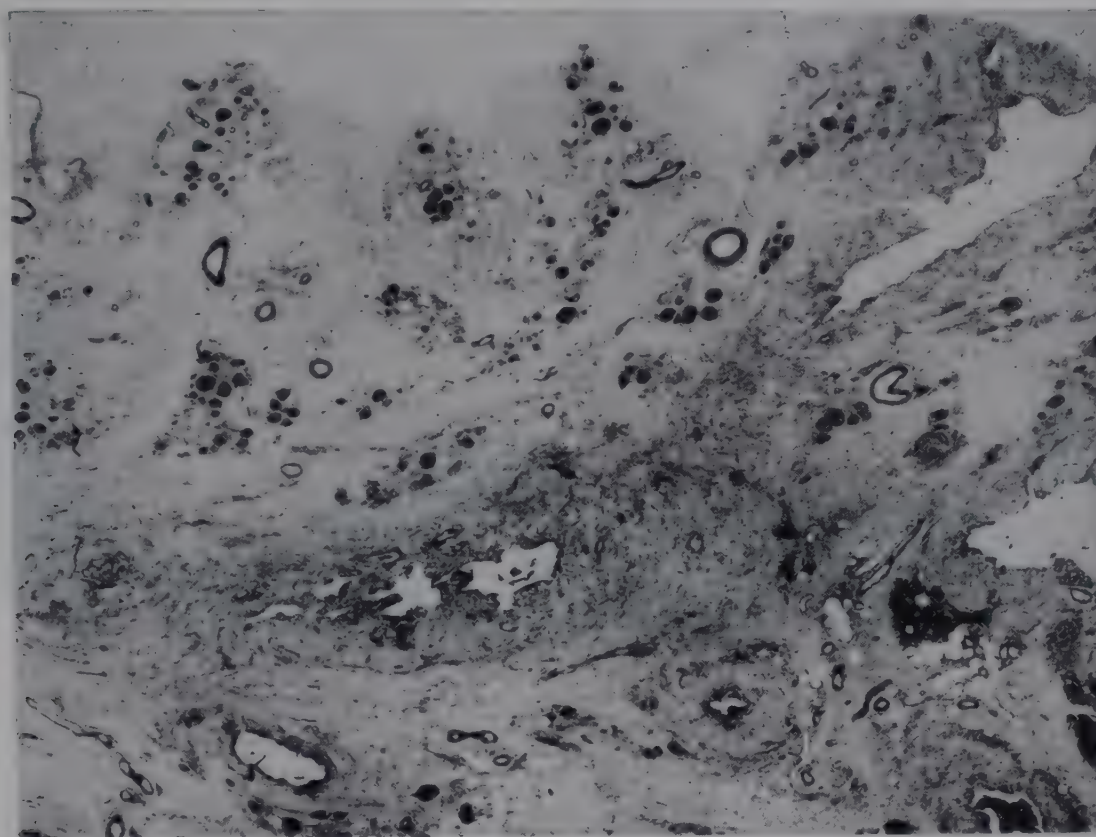


Fig. 293. Atrophy of the acinar tissue of the pancreas following obstruction of the duct. Note the isolated islands.

of the uterus are well known examples of this phenomenon.

Infection. The integrity of the walls of hollow viscera, particularly of the gastro-intestinal tract and the urinary tract, is in part maintained by the constant flow of fluid through the lumen. If fluid accumulates and contains bacteria, these bacteria are likely to invade the wall and enter the lymphatics and the blood stream. Pools of fluid, such as accumulate in the bladder behind an enlarged prostate, are likely to become infected, either from without or from the blood stream. The accumulation of ascitic fluid in the peritoneal cavity serves as a point of lowered resistance for the action of bacteria in the blood. In the case of calculi contained within a hollow viscus, pressure on the wall may lead to the formation of a decubital ulcer through which

inadequate muscle and elastic tissue within the wall, dilatation is irreversible. An example of the former is the gastro-intestinal tract and of the latter, the biliary tract. Thus, the finding of a dilated common bile duct is anatomic evidence that at one time there was an obstruction.

Localized Evaginations of Hollow Viscera

The lumen of a hollow viscus may be enlarged in a local area or segment. In the alimentary canal and urinary tract focal evaginations are known as "diverticula." In the circulatory system they are termed "aneurysms." In the respiratory tract the general designation is "ectasia," and the specific process "bronchiectasis." All are caused by a lesion which weakens the wall in a relatively small

area, acting in combination with a physical force to cause the area to extend into the surrounding tissue.

Types of Diverticula. A diverticulum may be formed by evagination of the entire thickness of the wall, or by protrusion of the inner layers of the wall through a defect in the outer layers. The former is known as a "true diverticulum," and frequently is congenital in origin. The latter is a "false diverticulum" and is usually acquired in origin. An example of the former is Meckel's diverticulum of the small intestine, and of the latter the diverticula about the major duodenal papilla. The physical force necessary to form the diverticulum may be exerted from within or from without. When the force is furnished by pressure from within the lumen, the term "pulsion diver-

lengthened and dilated to form a large, tortuous vessel, as occurs in the temporal artery, it is known as a "serpentine aneurysm." More localized types are qualified as "saccular," "fusiform," or "cylindrical," depending on the shape of the sac.

Types of Bronchiectasis. Bronchiectasis is usually classified, according to the shape of the dilated lumen, as "saccular," "cylindrical," or "fusiform."

Causes of Evagination. In all hollow viscera, the strength of the wall to resist the internal pressure is almost entirely contributed by the elastic tissue and muscular tissue. In arteries these two are concentrated in the media of the vessel, and any loss of the integrity or continuity of the media will lead to significant weakening. In the intestines and



Fig. 294. Diverticulum of the small intestine.

ticulum" is used. If the force is the contraction or pull of fibrous tissue on the outside, the diagnosis is "traction diverticulum."

Types of Aneurysms. A true aneurysm is a localized dilatation in which all or any part of the wall of the sac is composed of the original vascular wall. A false aneurysm is a sac in which the wall is constituted entirely from the surrounding tissue. Thus, after a bullet or stab wound into an artery, the escaped blood may remain in contact with the lumen of the vessel, and hollow out a sac in the adjacent tissue. If the false aneurysmal sac opens on one side into an artery and on the other into a vein, the lesion is known as an "arteriovenous aneurysm" or "arteriovenous fistula." Multiple arteriovenous aneurysms with the formation of a mass of dilated arteries and veins constitute the "cirroid aneurysm."

If the aneurysmal space is formed within the wall of the artery by splitting of the media, the condition is designated as a "dissecting aneurysm." If a long segment of an artery is

in the ureters and bladder, the elastic tissue is more diffuse, but the muscle is concentrated in one or more definite layers. In the bronchi the muscle and elastic fibers are concentrated in a thin layer in the mucosa.

Lesions. It is assumed that all the normal walls of the hollow viscera of the animal organisms are able to withstand far higher pressures than are ever present. It follows then that there must be some lesion of the wall before an evagination can occur. The general types of lesions are congenital (total or partial absence of the muscularis or media in a focal area), an intrinsic disease of the muscularis or media leading to local destruction of muscle and elastic tissue, and an extrinsic disease of the surrounding tissue resulting in erosion and destruction of a part of the wall from without.

CONGENITAL ABSENCE OF MUSCULARIS OR MEDIA. In the intestine the ducts from the intestinal glands and the arteries and the veins must penetrate the muscularis to reach the mucosa. At the point of penetration, there is a

defect in the muscularis through which, under increased pressure, the mucosa and submucosa may evaginate to form the usual diverticula of the small and large intestine. Similarly, in the small aneurysms of the cerebral arteries that form in the angle of the branches, it appears that a congenital absence of the media is the basic cause of the weakened wall.

INTRINSIC DISEASE OF MUSCULARIS OR MEDIA. The type of diverticulum or aneurysm based on intrinsic disease of the muscularis or media is best illustrated by syphilitic aneurysm of the ascending aorta. In this condition there is inflammation of the adventitia and media with replacement of the normally strong muscle and elastic fibers by weak fibrous tissue. At some points the loss of strength is so

great that the blood pressure within the aorta pushes the wall outward to form a saccular aneurysm. If the medial destruction is more widespread, the entire wall gives way to form a cylindrical or fusiform aneurysm.

EXTRINSIC DISEASE OF SURROUNDING TISSUE. Partial erosion of the wall of an artery from without is relatively uncommon except in the walls of tuberculous cavities of the lungs. It is probable that in most tuberculous patients who die of an exsanguinating hematemesis, the source of the hemorrhage is a perforation of a small aneurysm in the wall of the cavity. Caseation and ulceration in the lining of the cavity destroy the outer layers of the arterial wall, and the intima bulges to form a thin aneurysmal sac.

LXXVI

*Destructive and Reparative Processes—Cirrhosis of Liver,
Necrosis of Liver*

Probably no other organ of the body has as many varied and complex functions as the liver. Several factors make it impossible, however, to test the functional capacity of the liver by one or more of these metabolic processes: (1) The capacity of the liver to carry on its many functions is greatly in excess of the normal needs of the organism. (2) The capacity of the liver to perform its functions depends on many factors, and may change with extreme rapidity. (3) A decrease in one of the functions of the liver does not necessarily mean that all functions, or any one of its many functions, are equally impaired, or even injured at all. (4) Most of the functions of the liver are so intimately associated and correlated with the physiologic activity of other organs and tissues that it is difficult or impossible to delineate definitely the hepatic factors. (5) The liver maintains all of its known, and therefore measurable, functions at a normal level with extreme tenacity (Mann).

With this broad view it is apparent that any test of hepatic function must be interrupted in general terms. Further, a decreased function, as measured by any one test or combination of tests, probably indicates that there already exists a severe degree of damage to the liver. Serial tests over a period of days or weeks may point to a trend, and be a valuable guide to prognosis in that they will demonstrate whether the damage is increasing or decreasing.

The experimental studies of Mann and his associates have been of the greatest value in evaluating the hepatic function in terms of hepatic damage. They and others found that on total removal of the liver several important

physiologic processes immediately ceased: maintenance of the normal level of the blood sugar, formation of urea, oxidation of uric acid to allantoin, deamination of amino acids, formation of prothrombin, fibrinogen, and plasma albumin, and formation and destruction of the bile salts. These processes may be looked upon as exclusive functions of the liver, not carried on by any other organ. Other physiologic processes were modified: the ability to store injected or ingested sugars, and the detoxication of administered substances.

Despite the failure to secure precise correlation of structure and function in laboratory and diagnostic studies, certain tests have been of immense value in clinical medicine as indicators of prognosis and operability. Thus Graham found that by postponing operation on all persons with over 50 per cent retention of injected phenoltetraiodophthalein in the serum, the postoperative mortality of cholecystectomy was reduced from 6.5 per cent to 0.5 per cent, and of operation on the common bile duct from 7.7 per cent to 2.0 per cent. The same striking results have been reported for operative procedures on the thyroid (Boyce and McFetridge).

*Physiology of the Liver in Relation to
Disease*

BILE PIGMENTS

Formation of the Bile Pigments. From the earliest days of dissection it was noted that the bile in the biliary ducts and in the intestine apparently had its origin in the liver, and it was natural to assume that the cells of the liver made all of the constituents of bile.

Virchow first cast doubt on this conclusion by demonstrating that a pigment having certain physical and chemical properties characteristic of bilirubin could frequently be found at the site of old hemorrhages. He named this pigment "hematoidin." Since then many other investigators have made the same observation, and chemical studies leave little doubt that hematoidin, if not identical with bilirubin, is at least a chemical isomer (Rich and Bumstead). The concept that bile pigment could be formed in tissues other than the liver received a severe setback, however, in the now classical experiments of Minkowski and Naunyn. They demonstrated that a goose from which the liver had been removed did not show an accumulation of bile pigments in the blood. The experiments were undertaken in birds because at that time hepatectomy in mammals was not technically possible. Because of the renown of these two investigators, their results were immediately accepted and not questioned for almost fifty years. There thus arose the dictum, "Without the liver, no jaundice."

About 1920 a number of American investigators became interested in this problem, notably Whipple, Rich, and Mann. The work of Minkowski and Naunyn had been repeatedly confirmed, but the question arose: Was this observation in birds applicable to mammals? There were several clinical studies which indicated that it was not. For example, in acute yellow atrophy, in which there is complete destruction, or almost complete destruction, of the hepatic cells, the patient shows increasing jaundice in direct proportion to the amount of destruction of liver. Whipple and Hooper first undertook to remove the liver of a mammal from the circulation by placing ligatures about it. At the end of four or five hours there was no demonstrable clinical or chemical jaundice, and the thesis of Minkowski and Naunyn was apparently supported for mammals. Soon thereafter Rich injected India ink into dogs which had been prepared according to the technique of Whipple and Hooper. He found that the injected ink was phagocytized by the Kupffer cells of the liver, proving conclusively that this technique did not entirely remove the liver from the circulation.

Mann had devised a method for extirpating the liver from dogs without interfering with

the circulation in the remainder of the body. These animals lived for from two to four days if given proper supportive therapy. Mann, Bollman, and Magath applied this technique to a study of the origin of the bile pigments. They found that in the hepatectomized dog there was an appreciable increase in the amount of bile pigment in the plasma within three to six hours after the removal of the liver. With these studies there seemed little doubt that jaundice could occur in the entire absence of the liver, and that therefore the bile pigments were made by some other cell than the hepatic cells. Some still objected that the technique for the removal of the liver carried out in three stages allowed a compensatory mechanism to undergo hypertrophy. Rich later devised a method for the removal of the liver in one stage, and observed the appearance of the bile pigments within a few hours.

Following the observations of Virchow, Langhans in 1870 had observed that wandering phagocytic cells surround masses of blood formed by hemorrhage or by injection, and ingest the red blood cells. As the knowledge developed that these phagocytic cells are only one type of a great group, designated as the "reticulo-endothelial system," it was proposed that the members of this system of cells are responsible for the breakdown of hemoglobin into the bile pigments. This was finally demonstrated in vitro by Rich. Fresh red blood cells were added to tissue cultures of wandering phagocytic cells, and the formation of crystals of bilirubin from the ingested red cells was followed continuously under the microscope. There remained only to explain the original observations in geese, in sharp contrast with the latter studies in mammals. Histologic studies of the tissues of geese and of all birds clearly showed that almost the entire reticulo-endothelial system of birds is concentrated in the liver, and that hepatectomy in these animals removes not only the hepatic cells but all of the cells capable of destroying hemoglobin. In mammals this is not true, since the Kupffer cells represent only a part of the reticulo-endothelial system, and sufficient cells remain after hepatectomy to form the normal amounts of bile pigment.

Excretion of the Bile Pigments. Jaundice. The function of the hepatic cells in relation to the bile pigment is one of simple excretion.

The pigment in the blood is selectively removed by the cells of the liver and excreted into the bile ducts. It is a logical deduction that jaundice, an increase of the bile pigments in the tissues and blood, must result from either the failure of the liver cells to remove the bilirubin from the blood, or from obstruction of the excretory ducts, so that the bile cannot enter the intestine.

Jaundice in Ductal Obstruction. Jaundice resulting from obstruction of the bile ducts

facts, and may be discarded as a cause of jaundice. The second condition, *increased production of bilirubin* above the excretory ability of the normal liver, also finds little support in studies of actual disease. In fact, there are two lines of indirect evidence against it: (1) the normal liver is able to excrete much more bilirubin than is ordinarily delivered to it, and (2) diseases in which there is excessive formation of bilirubin are almost always those which tend to impair the excretory power of

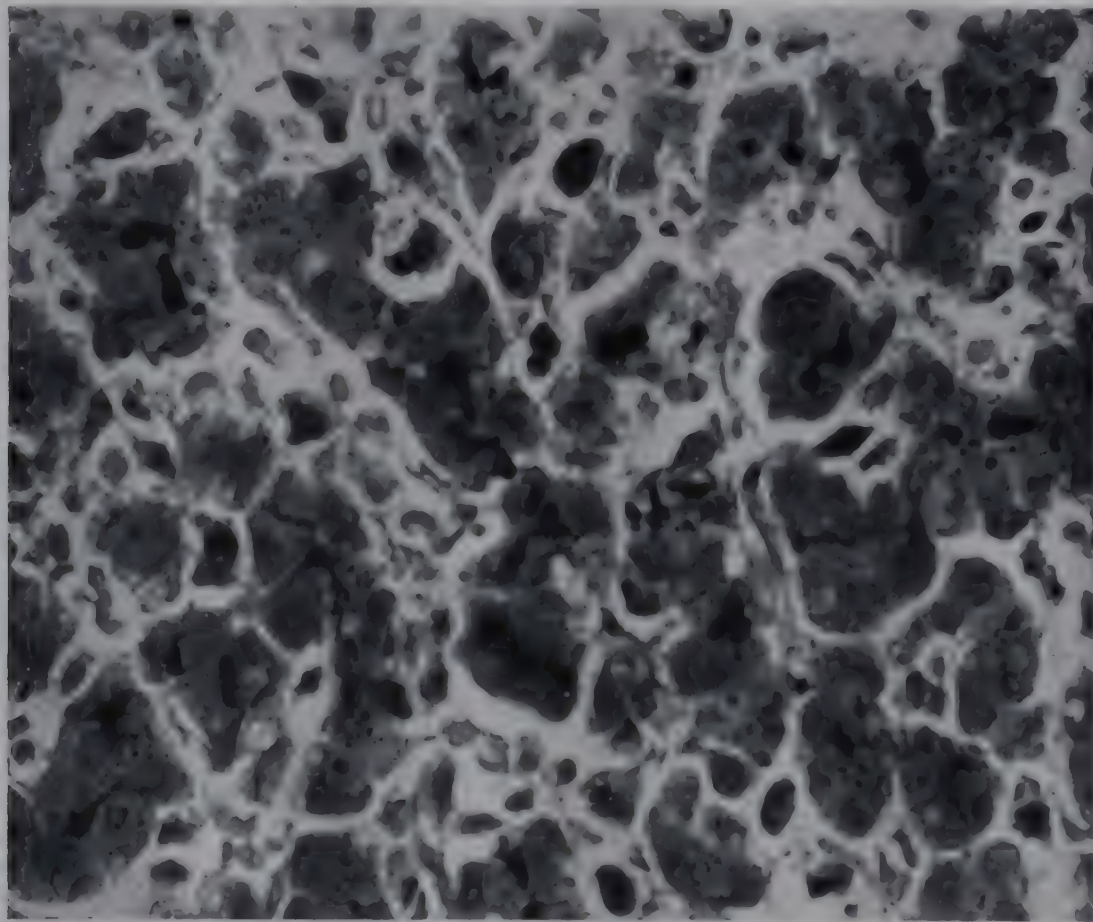


Fig. 295. Dilatation and plugging of the bile canaliculi in obstructive jaundice.

by calculi, tumors, or masses of inflammatory tissue is readily understandable if the greater part of the excretory system is blocked (see p. 620 on obstructive biliary cirrhosis). The bile pigments, bile salts, cholesterol, and other constituents are excreted by the liver cells, and enter the dilated excretory system, from which they are reabsorbed into the blood stream and continuously accumulate there.

Jaundice in Absence of Ductal Obstruction. There are three possible causes of jaundice occurring in the absence of ductal obstruction: (1) the threshold of the liver for the excretion of bilirubin is raised; (2) bilirubin is formed more rapidly than the liver can excrete it; and (3) the excretory mechanism of the liver is disturbed, so that the bilirubin cannot be excreted. The first condition, *increased threshold*, finds no support in observed

the liver. There remains then only the third postulate, a *disturbance in the excretory mechanism*, as an acceptable explanation of jaundice not caused by obstruction of the excretory ducts. In some instances, the damaged liver is called on to excrete only normal amounts of bilirubin, while in others there is an excessive amount. It is obvious that whether or not jaundice occurs in any case depends upon the balance between the amount of bilirubin delivered to the liver for excretion and the capacity of the liver to excrete it (Rich).

The Metabolism of the Bile Pigments. Clinical Tests for Jaundice. After formation in the reticulo-endothelial cells and excretion by the hepatic cells, the bile normally enters the gastro-intestinal tract, where at least three things may occur: some of the bilirubin is reabsorbed into the blood stream and taken

back to the liver for excretion; a smaller amount is converted by oxidation into urobilin, which is also absorbed and reexcreted by the liver and kidney; a third fraction is lost in the stool. When the excretory ducts are obstructed, all of the constituents of the bile are excreted by the liver, but are directly absorbed into the blood stream without passage into the intestine. The application of Ehrlich's diazo reaction as a test for bilirubin in albuminous fluids is helpful. Bile pigments which have been reabsorbed from the bile ducts as a result of obstruction give an immediate reaction with the diazo reagents. On the other hand, bilirubin which has never been excreted by the liver because of the failure of the excretory mechanism of the hepatic cells gives a delayed reaction. These are known

Classification of Jaundice. The grouping into retention jaundice and regurgitation jaundice as given by Rich seems to be the most practical and clinically valuable classification yet proposed. The basic differences in these two types are shown in Table 27.

Retention Jaundice. In this type, (1) the bilirubin in the plasma gives the indirect van den Bergh reaction; (2) the stools contain an increased amount of bilirubin because in the face of the increased production of bilirubin, the liver is excreting more pigment than normal, even though it cannot excrete enough of the excess to prevent jaundice; and (3) the urine contains an increased amount of urobilin but not bilirubin, and is free from bile salts. The hepatic cells show some slight degenerative changes, but there is no wide-

TABLE 27. DIFFERENCES BETWEEN TYPES OF JAUNDICE

	Retention Jaundice	Regurgitation Jaundice
Cause	Overproduction of bilirubin plus subnormal function of the liver	Rupture of the bile canaliculi
Van den Bergh reaction	Indirect	Direct
Stools	Increased bilirubin	Decreased bilirubin
Urine	Urobilin	Bilirubin and bile salts

as the direct and the indirect van den Bergh reactions respectively (Bollman and Mann). The explanation of the immediate and the delayed reactions is probably that pure bilirubin added to an albuminous fluid is adsorbed by the protein and is not immediately available for chemical reaction. When there is also present in the blood quantities of bile salts and cholesterol, such as is the case when the bile ducts are obstructed, this adsorption is prevented, and the bilirubin is free to enter into an immediate union with the diazo reagent. Another important aid in determining the nature of any particular case of jaundice is the demonstration of the nature of the bile pigments in the urine. In obstruction of the excretory ducts, free bilirubin is present in the blood plasma, and may appear in the urine together with the bile salts. In contrast, when there is no obstruction of the ducts the bilirubin is bound to the plasma proteins and is not easily excreted in the urine. On the other hand, the urobilin formed in the gastro-intestinal tract is excreted and readily demon-

strated. spread necrosis, and the bile ducts are patent. The general causes are anoxemia resulting from anemia or chronic passive hyperemia; febrile diseases inducing anoxemia by anemia or by pulmonary consolidation; and immaturity of the liver cells in the newborn.

Regurgitation Jaundice. In this type, (1) the bilirubin in the plasma gives a direct van den Bergh reaction; (2) the stools contain less urobilin than normal because the bile is not entering the intestine in normal amounts; and (3) the urine contains bilirubin, since the direct reacting or unbound bilirubin of the plasma is excreted by the kidneys. Bile salts are usually present in the urine also. There is necrosis of the hepatic cells or obstruction of the bile ducts. The necrosis of the liver may be caused by chemical agents, by vegetable substances, by bacteria or viruses, by advanced degrees of anoxemia, and by many undetermined agents, as in acute yellow atrophy and cirrhosis. Obstruction of the ducts may involve the ducts within the liver or outside of liver. Lesions within the lumen of the ducts, pathologic change in the wall of the ducts, and

pressure on the ducts from adjacent tumors, abscesses, aneurysms, enlarged lymph nodes, and cysts are the more important conditions leading to obstruction.

BILE SALTS

The retention of the bile salts in the body and the absence or decrease of bile salts in the intestine are equally important in a consideration of the relation of bile salts (sodium glycocholate and taurocholate) to diseases of the liver and bile ducts.

The Formation and Destruction of Bile Salts. In hepatectomized animals and in patients or animals with severe hepatic damage, bile salts cannot be detected in any of the body tissues, fluids, or excreta. Under these same conditions, bile salts injected into the blood are excreted quantitatively into the urine. These two observations indicate clearly that the hepatic cells are responsible for both the formation and the destruction of the bile salts. By differential studies in dogs it may be shown that the ability to form bile salts is more easily impaired than the ability to destroy them (Mann). Under normal conditions the bile salts are formed in the liver cells through the influence of several controlling factors, notably diet (Whipple and Smith), and are excreted into the intestine through the bile ducts. In the intestine a considerable percentage is reabsorbed and carried back to the liver, where they are either reexcreted or destroyed. One function of the reabsorbed bile salts is to act as a cholagogue or "pace-maker" for further excretion. Thus in animals, when only a small bile duct is cannulated and the greater part of the bile is allowed to enter the intestine, the quantitative secretion of fluid is about three times as copious as would be secured from the same segment of the liver if all the bile were diverted from the intestine (McMaster and Elman). In longstanding obstruction of the ducts, the formation of bile and bile salts is probably completely suppressed, both by the absence of the cholagogue and by the hepatic damage. This might be looked upon as analogous to the process of pyelovenous backflow in the kidney that alleviates the rapid accumulation of urine in hydronephrosis.

Toxicity of Bile Salts. Secondary Effects of Retention. The occurrence of severe nervous manifestations and other systemic symptoms

in the course of diseases in which icterus is a predominant feature gave rise, in an early period, to experimental investigations of the effect of bile on the animal organism. It was demonstrated that the bile salts are extremely toxic, and that intravenous injection in mammals frequently leads to death (Meltzer and Salant). Since most diseases that produce retention of bile also set in motion physiologic and pathologic processes which depress the formation of the bile salts, it is probable that most of the symptoms referred to result from hepatic insufficiency.

Secondary Effects of the Absence of Bile Salts in the Intestine. Hemorrhagic Diathesis. Bile salts are necessary for the proper digestion and absorption of the fats and the fat-soluble vitamins. From a practical standpoint the most important of these is vitamin K. In the absence of bile, vitamin K is not absorbed, and when the store of the vitamin is depleted the formation of prothrombin ceases. An additional factor in most patients is the hepatic damage incident to obstruction of the ducts or resulting from agents which impair the ability of the liver to make prothrombin. As prothrombin is constantly removed from the blood (Andrus, Lord, and Kauer), there is a gradual or precipitous fall, and the patient is likely to show a tendency to bleed from the skin and mucous membranes. There may be larger hemorrhages into the muscles or viscera. A series of tests with vitamin K serves to determine the exact nature of the defective metabolism, and the extent of the hepatic damage. If vitamin K and bile salts are administered by mouth to a patient with regurgitation jaundice and hypoprothrombinemia, and a prompt increase of the plasma prothrombin results, it may be concluded that the function of the liver (for this one metabolic process) is not impaired, and that the defect is in the absorption of the vitamin. If ingestion does not give a response, a water-soluble form of the vitamin is given intravenously or intramuscularly. The prompt increase of prothrombin under these conditions indicates that absorption was faulty and that the hepatic formation is adequate. On the other hand, a failure of the liver to make prothrombin after parenteral administration of vitamin K points to severe damage of the liver as the cause of the hypoprothrombinemia (Lord and Andrus).

METABOLIC ACTIVITIES OF THE LIVER

Metabolism of Carbohydrates. The most important and outstanding functions of the liver in the metabolism of carbohydrates are the storage of glycogen in the hepatic cells and the conversion of amino acids into sugar.

Maintenance of the Blood Sugar. Immediately after removal of the liver in animals, the blood sugar level begins to decrease progressively, and if some form of simple carbohydrate is not injected, symptoms of hypoglycemia soon develop. The administration of anesthetics or epinephrine, and asphyxia, have no effect. Glycosuria induced by phlorhizin in hepatectomized animals results in a precipitous fall in the blood sugar, from which there is no recovery. The total production of heat and the respiratory quotient decrease, and the storage of glycogen may go as low as 50 per cent of normal. The cause of all of these phenomena is probably that the liver is the largest storehouse of available sugar, and as the amount in the body fluids and tissues at the moment of hepatectomy is burned, there is no further source (Mann).

Clinical Applications. It follows that in severe damage to the liver in man there is a low blood sugar value, and if the disease is progressive there is a decreasing value. In less severe destruction of the liver numerous attempts have been made to devise a test to determine the ability of the liver to remove injected or ingested carbohydrates from the blood. Unfortunately, dextrose is also stored in considerable quantities by other tissues (muscles), and cannot be reliably used for a test. With levulose and galactose some measure of success has been reported. A normal person is able to assimilate a 40 gm. oral dose of galactose with loss of less than 2.5 to 3 gm. of sugar in the urine in five hours. With hepatic damage the liver is unable to convert the galactose to glycogen, and there is a greater degree of galactosuria (Shay and Schloss).

Metabolism of Proteins. As pointed out, the functions of the liver in the metabolism of proteins are deaminization of amino acids, formation of urea, oxidation of uric acid to allantoin, and formation of fibrinogen, serum albumin, and prothrombin.

Clinical Applications. The impairment or failure of these activities results in a decrease in the blood urea, plasma fibrinogen, plasma

proteins (almost entirely by a fall in albumin), and plasma prothrombin; and an increase of blood uric acid and plasma amino-nitrogen. These changes in the blood are reflected in the urine by an increased urinary excretion of amino-nitrogen and ammonia, and a decreased excretion of urea. The blood non-protein nitrogen varies, depending on the relative decrease in the formation of urea and increase of amino-nitrogen, and the ability of the kidney to excrete the increased amount of nitrogen. Under any conditions the percentage of urea nitrogen in the total nonprotein nitrogen of the blood is significantly decreased. In disease of the liver in man this full physiologic disturbance is rarely seen, but in acute yellow atrophy and other advanced lesions one or more of the conditions may be demonstrated. The relation of the formation of plasma albumin is of greater clinical import. Many patients with cirrhosis of the liver have a low value for plasma albumin, and it is probable that the consequent decrease of the plasma osmotic pressure plays a role in the formation of ascites and edema (Myers and Keefer). The slower regeneration of albumin after plasmapheresis in dogs with hepatic damage also points to a relation of the liver to the maintenance of the plasma albumin (Kerr, Hurwitz, and Whipple).

Metabolism of Lipids. There are few precise studies on the relation of hepatic damage to measurable changes in the lipids of the blood. In general, obstruction of the bile ducts leads to an elevation of blood cholesterol. In lesions involving necrosis of the liver the total cholesterol is normal or decreased. Of probably greater significance is the marked decrease, or even complete absence, of cholesterol esters in the latter condition (Epstein and Greenspan).

Miscellaneous Excretory, Conjugation, and Detoxication Functions of the Liver. A great variety of actual or supposed physiologic activities of the liver have been used to test the function of the liver in both man and animals. The most notable of these are (1) the ability of the liver to excrete certain dyes (Snell and Magath); (2) the influence of the plasma proteins on the stability of certain colloidal systems (Takata-Ara test) (Magath); (3) the elevation of blood phosphatase in jaundice associated with obstruction of the bile ducts (Rothman, Meranze, and Mer-

anze); and (4) the ability of the liver to synthesize amino-acetic acid and conjugate it with benzoic acid to form hippuric acid (Boyce and McFetridge).

Necrosis of the Liver

Anatomy. The liver differs from most other organs in the character of the *blood supply*, a factor which probably materially influences the nature of the pathologic changes in it. The portal vein draining the greater part of the organs within the abdomen enters the hilum and branches, until the smaller veins in the portal spaces give rise to the sinusoids between the liver cells. The hepatic artery follows the branches of the portal vein, but only a small amount of the total blood in intimate contact with the liver cells is of arterial origin. This suggests that the liver should respond to anoxemia earlier and to a greater extent than would many other organs supplied with pure arterial blood.

For the purpose of evaluation of disease, the liver is conveniently divided into hepatic *lobules*. The center of a hepatic lobule is occupied by the central vein, a tributary of the hepatic veins. The periphery is formed by the immediately adjacent portal spaces. Thus the pathologist distinguishes in the liver a *central zone*, a *midzone*, and a *peripheral zone*, based on a central vein. The peripheral zone is composed of the liver cells immediately about the portal spaces. The hepatic *cells* are polygonal, with six or more sides, and are arranged in double columns, extending radially from the central vein to the portal space. The space between the individual liver cells constitutes the *intercellular bile canaliculi*. The adjacent columns of liver cells are separated from one another by the *sinusoids* connecting the portal vein and hepatic artery with the central vein. These sinusoids are lined by two types of cells, ordinary *endothelial cells* with small hyperchromatic nuclei, and an elongated, thin mass of cytoplasm. The second cellular type is the *stellate cell of Kupffer*, in which the nucleus is larger and less chromatic, and usually has a prominent nucleolus. The cytoplasm of the Kupffer cell is abundant, and within it there are frequently small inclusions of partially digested red blood cells.

Separating the liver cells from the Kupffer and endothelial cells there is a delicate *membrane of collagen*, with an occasional fibro-

blastic cell. In certain pathologic conditions not well understood, this membrane of collagen becomes separated from the cords of liver cells, and there is deposited in the space a granular, acidophilic debris, presumably protein-rich fluid. This condition is known as "serous hepatitis," and is considered by many to be the histologic evidence of the slightest degree of hepatic damage. The *portal canals* are made up of a collagen-poor connective tissue in which the vessels and nerves are embedded, together with a few lymphocytes and mononuclear cells. The wandering cells, and to some extent the relative amount of collagen, increase progressively with increasing age. Thus the portal canals in a person of seventy are larger and more heavily infiltrated with lymphocytes than those of a person of twenty.

Types of Injurious Agents. An injurious agent may be brought to the liver through the portal vein, through the hepatic artery, or through the bile ducts, in addition to the always possible direct implantation from the outside environment through a wound. This agent may be a *substance soluble in the blood stream* taken with the food, as a therapeutic or suicidal agent. The *substance may be in particulate form*, such as particles of carbon that escape from anthracotic lymph nodes by rupture into the pulmonary veins. Under these conditions the particles are removed from the blood stream and ingested by the Kupffer cells, and held at that point or transported to the portal spaces—anthracosis of the liver. Under exceptional circumstances the carbon and silica portions may accumulate to the point where there is excessive production of connective tissue in response to their presence in a manner identical with fibrosis of the lung in response to the same substances—anthracotic cirrhosis of the liver (Welch).

Colloidal particles such as acacia injected for the treatment of hypoproteinemia in nephrosis are similarly removed by the Kupffer cells, and, in this instance, stored in the hepatic cells. The Kupffer cells of the sinusoids also phagocytize *red blood cells* from another animal or from a foreign species, as well as *bacteria*. With bacteria, unless they are in overwhelming numbers, there results complete autolysis of the bacterial cell. The ability of the liver to remove bacteria from the blood stream is of great importance in the evaluation of the defense mechanism of the body.

When bacteria are excessively numerous, or of high virulence, they multiply in these organs and reappear in the blood stream after from five to seven hours. The Kupffer cells and the hepatic cells are probably also able to modify injected *foreign protein*. Thus if a protein is perfused through a living liver and then injected into a sensitized animal, anaphylactic shock does not occur, or it is greatly modified (Opie).

Focal Necrosis. By focal necrosis is meant the presence in the liver of small, usually spherical masses of necrotic cells, distributed throughout the organ without regard for the

ward for from one-fourth to one-half the distance to the portal canal. Within the area the sinusoids are dilated and filled with red blood cells. The columns of liver cells vary from simple disruption and beginning necrosis of individual cells to complete disappearance of all cellular elements of the columns. This condition is seen in a wide variety of infectious diseases, in chronic passive hyperemia, and following the administration of chloroform, carbon tetrachloride, or other hepatotoxic chemicals.

Midzonal Necrosis of the Liver. The typical example of midzonal necrosis is seen in yellow

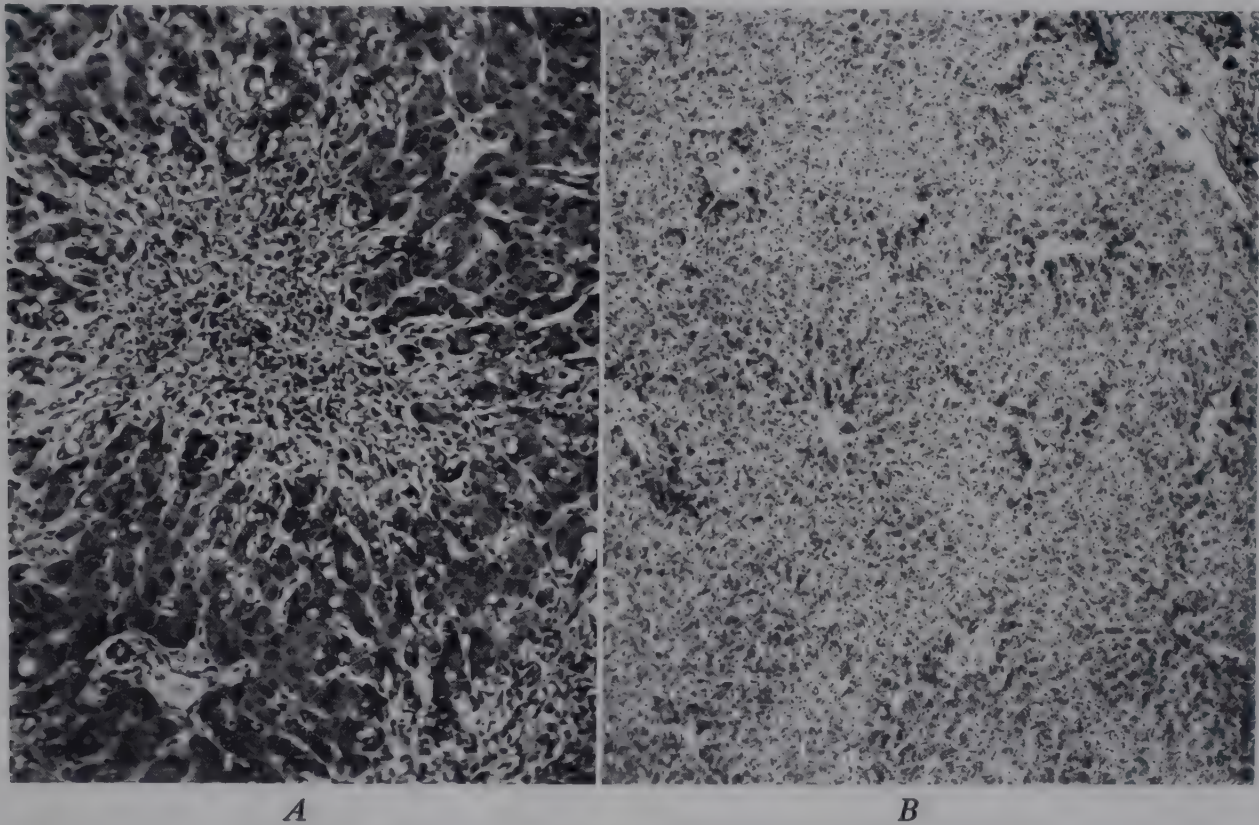


Fig. 296. Zonal necrosis. A, Central. B, Midzonal.

lobular architecture. The usual focus is not grossly visible. The typical example of focal necrosis is that seen in typhoid fever. Careful analysis shows that the sinusoids of the foci are filled with large mononuclear cells containing phagocytized red cells and lymphocytes. The liver cells are in all stages of necrosis and autolysis. There is a slight infiltration of the area with polymorphonuclear leukocytes. At a later stage the mononuclear cells also undergo necrosis, and there is fibrin in the area (Mallory). Similar lesions are seen in many other infectious diseases, notably poliomyelitis and tularemia.

Zonal Necrosis. *Central Necrosis of the Liver.* In central necrosis of the liver there is partial or complete destruction of the liver cells about the central vein extending out-

ward. The part of the columns of liver cells midway between the portal canal and the central vein shows necrosis, with only slight cellular infiltration with mononuclear cells and polymorphonuclear leukocytes. The sinusoids are correspondingly dilated (Klotz and Belt).

Peripheral Necrosis of the Liver. In eclampsia the hepatic cells in the peripheral portion of the hepatic lobule—that is, those cells immediately about the portal spaces—undergo necrosis. The sinusoids frequently are filled with hyaline thrombi, and the cytoplasm of the liver cells is swollen and hyaline. The nuclei undergo karyolysis or pyknosis. Occasionally in infectious diseases there is peripheral necrosis.

The Mechanism of Selective Hepatic Necrosis. Of great interest are the reasons why

certain poisonous substances exert selective action on only certain parts of the lobule of the liver.

Focal Necrosis. This may be satisfactorily explained on the basis of local blockage of sinusoids by large mononuclear cells. Mallory felt that these cells in typhoid fever wander into the mesenteric veins near the lesions in the intestine, and are brought as emboli to the sinusoids of the liver. A combination of the ischemia and the bacterial toxins induces necrosis of the adjacent hepatic cells.

Zonal Necrosis. The explanation of zonal necrosis is more difficult. On the basis of the distribution of the blood and the fact that the central areas are the farthest removed from the sources of blood, it may be assumed that central necrosis is associated with all conditions inducing anoxemia. This serves in large part to explain central necrosis in the infections and in chronic passive hyperemia. With the known chemical substances and certain unknown hepatotoxic agents, as in eclampsia, this explanation is inadequate. It is logical to assume that a particular cell in the body is damaged by a soluble toxin in the blood stream, because it selectively removes that substance from the blood and concentrates it within the cytoplasm or nucleus. It follows that chloroform brings about damage to the liver because it is removed from the blood and stored in the hepatic cells. Graham showed that any halogenated aliphatic hydrocarbon (bromoform, iodoform) is capable of inducing central necrosis of the liver. He further showed that the degree of hepatic damage is in direct proportion to the theoretical amount of the halogen acids that can be liberated by the toxic agent, and that the central part of the liver under these conditions becomes acid. It is possible that phosphorus similarly is converted into phosphoric acid. This demonstration serves to explain the mechanism of necrosis, but does not explain the fact that chloroform attacks the central area and phosphorus the peripheral area.

It is not unlikely that the functions of the central cells differ from those of the peripheral cells. Evidence for this is given by the almost selective elevation of uric acid in eclampsia in which only the peripheral cells are involved. Careful histochemical studies would be most useful in elucidating this problem.

Acute Yellow Atrophy. Postnecrotic Cirrhosis. Acute diffuse necrosis of the liver was first described under the title of acute yellow atrophy and was of unknown cause. Later it was observed after the administration of numerous drugs—chloroform as an anesthetic (Sheehan), salvarsan and other arsenicals (Snapper, Chin, and Lin), cinchophen and related atophan (MacBryde), sulfonamides (Cline), and petroleum products (Braunstein). A similar lesion is observed in pregnant women (Stander and Cadden) and in hyperthyroidism (Kerr and Rusk).

Although it cannot be denied that certain chemicals may produce massive necrosis of the liver, it seems likely that most if not all examples of acute yellow atrophy are infectious hepatitis or serum hepatitis (see p. 384).

Hepatic Death—Hepatorenal Syndrome

In some patients who die following operations on the biliary tract, liver or pancreas, there are no demonstrable postoperative complications of pneumonia, peritonitis, or other easily recognizable anatomic changes. These cases are conceivably divisible into two groups (Heyd): (1) those in which death occurs on the third to the sixth day with the outstanding sign of hyperpyrexia, and (2) those in which death occurs from the sixth to the tenth day with the signs and symptoms of uremia.

Pathologic Anatomy. At autopsy in both groups the liver is seen to be of normal size or slightly smaller, and friable. The liver cords are disrupted, and there is fatty degeneration and necrosis in individual liver cells. In the kidneys of the patients who die of uremia there are in addition fatty degeneration, cloudy swelling, and necrosis of the renal epithelium. In both types of patient there is likely to be extensive hemorrhage into the gastro-intestinal tract and numerous petechiae in the mucosa (Schutz, Helwig, and Kuhn).

Causal Factors and Pathogenesis. No entirely satisfactory explanation of these postoperative changes has yet been offered. A logical theory postulates that during the course of an operation a person with an already damaged liver may develop necrosis from the additional trauma of operative manipulation, and from the anesthetic and other therapeutic agents. The absorption of certain toxic sub-

stances from the necrotic cells disturbs the heat-regulating centers of the brain, and hyperpyrexia results. If the toxic agent is present in large amounts, or for a long period, there is necrosis of the renal epithelium and uremia (Schutz, Helwig, and Kuhn; Boyce and McFetridge).

Cirrhosis of the Liver

The term "cirrhosis" is applied to all sclerosed conditions of the liver, whether progressive or not, in which destruction of liver cells is associated with real or apparent increase of connective tissue stroma (Mallory; Karsner).

Classification of Cirrhosis. As with so many chronic progressive diseases, our knowledge of cirrhosis is not complete. We must, therefore, be satisfied at the moment with a classification based partly on anatomic and partly on causal grounds.

- A. Cirrhosis caused by mechanical factors
 - 1. Obstructive biliary cirrhosis
 - 2. Congestive cirrhosis
- B. Cirrhosis caused by living agents
 - 1. Colon bacillus cirrhosis
 - 2. Streptococcal cirrhosis
 - 3. Syphilitic cirrhosis (hepar lobatum)
 - 4. Schistosomal cirrhosis
 - 5. Postinfectious cirrhosis (epidemic and serum hepatitis)
- C. Cirrhosis caused by particulate matter
 - 1. Silicotic cirrhosis
- D. Cirrhosis of unknown cause
 - 1. Pigmentary cirrhosis (hemochromatosis)
 - 2. Nodular cirrhosis (Laennec)
 - 3. Unclassified types of cirrhosis

Hanot's biliary cirrhosis has been omitted in the belief that it is not a separate entity. Most, if not all, examples will be found on careful study to be the early stage of nodular cirrhosis with fatty metamorphosis, or colon bacillus cirrhosis.

Incidence. Cirrhosis in general is a disease of men of the fourth, fifth, and sixth decades of life, but each of the types has definite characteristics of incidence (Mallory). Nodular cirrhosis has its highest incidence in the fifth and sixth decades, pigmentary cirrhosis in the sixth, postinfectious cirrhosis in the sixth, syphilitic cirrhosis in the fifth, colon bacillus cirrhosis in the seventh, obstructive cirrhosis in the seventh, and unclassified cirrhosis in the sixth and seventh.

Clinicopathologic Correlation. General Effects of Portal Obstruction. Most of the signs and symptoms in cirrhosis depend on one of three factors: (1) decreased functional ability of the liver, (2) changes in the size of the liver, and (3) an increase of pressure in the portal venous system. The first of these has been discussed. Consideration will be given here to the latter two.

Size of Liver. The size of the liver in cirrhosis is related to (1) the ratio of regeneration to destruction, (2) the degree of fibrosis and contraction, (3) the presence and degree of an associated fatty metamorphosis, and (4) the presence and degree of a causal or an associated inflammation. Thus in post-infectious cirrhosis in which destruction is conspicuous and regeneration proceeds slowly, the liver is small early, and only after many months or years does it even approach normal size. On the other hand, in the acute stages of cirrhosis caused by the colon bacillus there is diffuse cholangitis and hepatitis with inflammatory exudation, and the liver is increased in size, often to twice normal. Similarly in cirrhosis associated with fatty metamorphosis, the greater the amount of fat the larger the liver, regardless of the degree of destruction and fibrosis.

Portal Obstruction. The increase of pressure in the portal venous system is responsible for the more important signs and symptoms and for most of the secondary pathologic changes in cirrhosis. The mechanism of its production has not been completely elucidated. Studies of the vascular tree by injection show some obstruction, but not sufficient to bring about long-continued hypertension (McIndoe). In vitro studies by perfusion have yielded interesting results. There is no essential difference between the velocity of perfused fluid through the portal vein of a normal liver and of a cirrhotic liver. On the other hand if a liver is perfused simultaneously through the portal vein and the hepatic artery, there is a significant decrease, as much as 50 per cent, in flow through the portal vein in cirrhotic livers. This suggests that numerous small arteriovenous communications are established in the cirrhotic liver, so that the hepatic pressure is transmitted to the major branches of the portal vein, which effectively raises the pressure and hinders the flow of blood through the portal vein (Dock).

DEVELOPMENT OF PASSIVE HYPEREMIA. The increase of portal pressure leads to chronic passive hyperemia of all structures drained by the portal vein. There is passive hyperemia of the spleen and of the greater part of the gastrointestinal tract. Anastomotic channels are established between the portal system and systemic system, in the esophagus, and in the hemorrhoidal area. The veins in these regions are dilated, and one of the not infrequent causes of death in cirrhosis of the liver is rupture of one of the esophageal varices.

EXPLANATION OF THE ASCITES. One of the most conspicuous manifestations of the chronic passive hyperemia is the accumulation of fluid in the peritoneal cavity. Two factors are probably responsible for this: increase of venous pressure, and decrease of plasma albumin. The plasma albumin is probably manufactured in the liver, and in extensive injury or damage, such as is present in most patients with cirrhosis, there is inadequate synthesis and a consequent hypoproteinemia (Post and Patek). Since the plasma albumin is largely responsible for the maintenance of the osmotic pressure of the blood, it follows that this physical property is decreased in value, and that fluid will leave the vessels. In most instances the decrease is not conspicuous, and the lowered osmotic pressure is not the sole cause of the development of ascites (Butt, Snell, and Keys). The occurrence of right-sided hydrothorax in cirrhosis is unexplained (Frothingham).

Gynecomastia in Cirrhosis. In a small percentage of patients with cirrhosis of the liver gynecomastia is present. An explanation of this is found in the inability of the cirrhotic liver to inactivate the estrogens. The resulting excess in active estrogen in the fluids of the body stimulates the breast to hyperplasia. In the urine of these persons there is a large amount of free estrogen, and only small amounts of androgen (Glass, Edmondson, and Soll). The same phenomenon serves to explain the arterial spiders of the skin (Bean).

Metabolism of Vitamin A. A cirrhotic liver contains less vitamin A than normal; the plasma of the patient is at a lower level and the administration of vitamin causes less elevation of the plasma value than it normally does (Ralli, Bauman, and Roberts).

Hepatolenticular Degeneration. Occasionally cirrhosis of the liver, identical with dif-

fuse nodular cirrhosis, is associated with degeneration in the lenticular nucleus of the brain. The condition is also known as "Wilson's disease." It is occasionally familial, and begins before the age of thirty. It is characterized by intention tremor, muscular hyper-tonia, masked facies, and occasionally tonic or colonic convulsions and some evidence of hepatic disease (Sweet, Gray, and Allen).

Causal Factors. Experimental Cirrhosis in Animals. The histologic appearance of the liver in cirrhosis has led many investigators to postulate that continued or intermittent damage to and necrosis of small parts of the liver result in fibrosis and the general picture of cirrhosis. An analysis of this theory is intimately tied up with the experimental production of the disease in animals, and the two topics will be discussed together.

Alcohol. From a study of clinical and autopsy material it is clear that from 5 to 6 per cent of persons addicted to the use of alcoholic beverages develop cirrhosis, and that 25 to 35 per cent of persons with cirrhosis give a definite history of the excessive consumption of alcoholic drinks. These figures suggest two conclusions: (1) that alcohol is not the sole cause of cirrhosis in man, and (2) that when alcohol is an accepted causal agent there must be other predisposing factors. It follows that if one is to use the term "alcoholic cirrhosis," anatomic criteria must be established to separate this type. Some investigators feel that this is possible. Thus, Hall and Morgan selected only the cases corresponding to the description of subacute cirrhosis, and found a history of the excessive use of alcohol in 75 per cent. The average age of death was 46.8 years, as compared to 60 years for all types of cirrhosis. Experimental investigations to support this idea have not been very helpful.

Connor and his associates found that the administration of alcohol to dogs and rabbits fed a high fat diet led to extreme fatty degeneration of the liver, and eventually to cirrhosis. The postulated mechanism is that alcohol interferes with the respiration of cells, especially with the utilization of sugar, and there is then an accumulation of fat in the liver cells. Connor suggested, however, that other factors, such as a deficient diet, must cause a basic defect for the alcohol to act on. Alcohol may therefore be considered to contribute to cir-

rhosis by reinforcing or accentuating the effects of other agents, or by producing degenerative changes in the hepatic cells, thereby rendering them more susceptible to injury (Moon).

Dietary Constituents. ROLE OF CARBOHYDRATES AND GLYCOGEN. A high carbohydrate diet and an adequate storage of glycogen in the liver increase the resistance of an animal to hepatotoxic agents, such as chloroform and phosphorus (Opie). Utilization of this fact by the surgeon has led to a significant reduction

perimental observations point to the great significance of fatty degeneration of the liver as the initial lesion of cirrhosis, and the importance of dietary substances controlling the deposition of fat, such as choline, cystine, casein, and a high fat diet, in causing cirrhosis.*

Carbohydrates and some components of the vitamin B complex are not the only dietary factors concerned with the liability of the liver to injury. Dogs fed a diet of 10 gm. of lard and 7 gm. of lean meat per kilogram per day

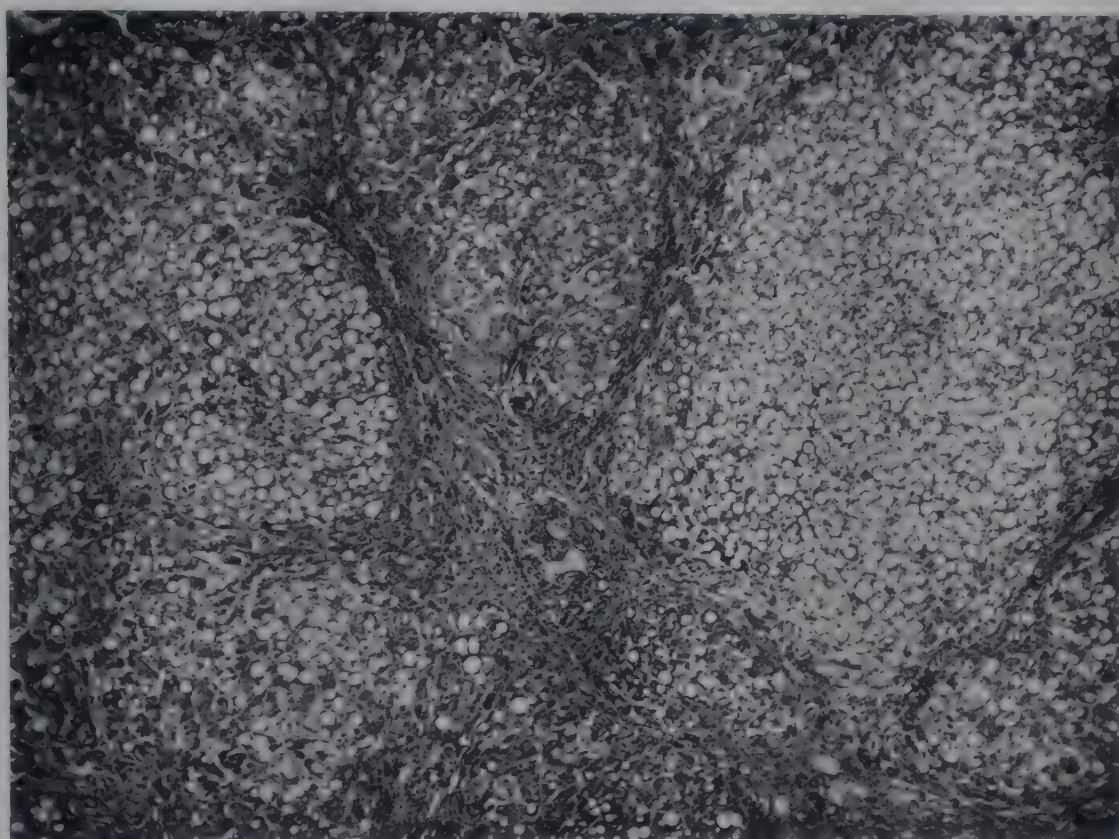


Fig. 297. Cirrhosis of liver with fatty metamorphosis.

in operative mortality following procedures on the biliary tract. A rabbit given small doses of lead arsenate does not develop cirrhosis of the liver if certain diets are fed—notably carrots and cabbage, potatoes, and white bread or brewers' yeast (VonGlahn and Flinn).

ROLE OF VITAMIN B. It has also been shown that rabbits fed a certain basal diet deficient in vitamin B, but not containing any known hepatotoxic agent, develop cirrhosis of the liver, and that this may be prevented by the addition of brewers' yeast. The active element in the yeast is not thiamine, riboflavin, pyridoxin, or nicotinic acid (Rich and Hamilton).

ROLE OF CHOLINE. Under similar conditions in rats the addition of choline reduces the incidence and severity of the hepatic injury, while the daily ingestion of small amounts of cystine greatly accentuates the degree of cirrhosis (György and Goldblatt). All of the ex-

will, in about a year, develop diffuse fibrosis of the liver in association with extreme fatty degeneration (Chaikoff and Connor).

ROLE OF PROTEIN. The significance of protein has been appreciated only recently. For example, a dog with a depletion of the bodily stores of protein is frequently unable to withstand fifteen to twenty minutes of inhalation of chloroform, while control dogs tolerate ninety minutes without appreciable hepatic damage (Miller and Whipple). It thus becomes apparent that the maintenance of an adequate diet is vital to the proper protection of the liver from hepatotoxic agents.

* See also the discussion of experimental tumors of the liver produced with butter yellow in the section on carcinoma of the liver, p. 617; of lipocaic deficiency in the section on diabetes, p. 871, and of a deficiency of choline in the chapter on vitamin deficiencies, p. 548.

ALCOHOLISM AND DIET. Evidence that this view, derived from animal experimentation, is applicable to man is given in a number of observations. A significant number of chronic alcoholic patients with cirrhosis show evidences of polyneuritis, based on the deficiency of thiamine (Wayburn and Guerard). Less commonly there are pellagrous dermatitis, glossitis, and anemia, pointing to other dietary deficiencies. The administration of a diet high in vitamins leads not only to an alleviation of the specific deficiencies, but also to a general improvement in the symptoms related to hepatic damage (Patek and Post). It is ap-

already damaged by another agent. A type of infectious cirrhosis associated with streptococci has been described (MacMahon and Mallory).

Miscellaneous Hepatotoxic Agents. Many other substances are known to produce either necrosis or cirrhosis of the liver in experimental animals, but the proof is lacking that they are of importance in man. The more notable of these are phosphorus (Mallory), arsenic (VonGlahn, Flinn, and Kein), lead (Mallory), copper (Mallory, Parker, and Nye), manganese (Findlay), silica (Gye and Purdy), tar (Murayama), chloroform



Fig. 298. Cut surface of liver in diffuse nodular cirrhosis. (MacCallum.)

parent that the continued ingestion of alcohol is not the direct cause of the vitamin deficiency, but rather that the addiction to alcoholic beverages usually involves the consumption of an inadequate diet (Blankenhorn and Spies).

Infection. In early studies of experimental cirrhosis Opie showed that a combination of intoxication with chloroform and an intravenous injection of *Escherichia coli* leads to a greater degree of cirrhosis than either agent produces alone. Direct application of this experiment to the conditions in man is difficult, but there is some evidence that one infectious disease, syphilis, may be related to cirrhosis. Several studies have shown that the incidence of cirrhosis is distinctly higher in chronic alcoholism and syphilis than in either condition alone (Schumacher). Again the facts indicate a hypothesis that alcohol may act on a liver

(Schultz, Hall, and Baker), and carbon tetrachloride (Lamson and Wing).

Summary. It is evident that no one single causative factor is responsible for cirrhosis. Rather, a host of agents acting in combination bring about progressive destruction of hepatic cells and replacement by fibrous tissue. The agents are divisible into two classes: those lowering the resistance of the liver (deficiencies of protein, carbohydrate, and vitamins), and those leading to a necrosis of the cells of the liver (hepatotoxic agents such as alcohol, phosphorus, lead, and arsenic). Much more study is needed on this complex subject.

Diffuse Nodular Cirrhosis

"Diffuse nodular cirrhosis" is the preferred designation for the disease variously known as "Laennec's cirrhosis," "alcoholic cirrhosis," and "hobnailed liver."

Pathologic Anatomy. Gross Examination.

The liver may be enlarged, normal, or decreased in size. The color is a yellow or tawny brown. The capsule is usually not thickened, or only slightly so, and there are rarely adhesions to the surrounding viscera. The most characteristic features are an increased firmness and a gross nodularity of the surface. The nodules vary from 1 to 20 mm. in diameter and project above the surface. On section, the substance cuts with increased resistance, and the nodularity is easily discernible. Each nodule appears as a roughly circular mass of yellow or brown soft tissue, projecting slightly above the cut surface. Between the nodules is a firm, fibrillar, gray or bluish gray connective tissue.

The larger bile ducts and the branches of the portal vein and hepatic artery show no pathologic change. In most patients there are the alterations consequent to portal obstruction. The spleen is enlarged, firm, and dark purple. The peritoneal cavity contains a variable quantity of clear, yellow fluid, and the peritoneum may be slightly thickened and opaque. Occasionally the fluid is cloudy, and the peritoneum is covered by an exudate, the result of an infection brought by the blood to a tissue of lowered resistance, or introduced by the needle used in paracentesis, either by perforation of the intestine or from without. The wall of the intestine is edematous, and the blood vessels are prominent. In the esophagus there are usually varices, and one or more may have ruptured through an ulcer in the mucosa. If rupture has occurred, the lumen of the stomach and intestine contains bright red or brown blood.

Microscopic Examination. The microscopic appearance varies from that of an active progressive disease to that of a quiescent, apparently healed lesion. In the active form the hepatic cells, especially those along the edges of the nodules, show degenerative and regenerative changes. The outlines of the nodules are not sharp, and at many points there is a defect filled with a loose connective tissue. Some hepatic cells are granular and filled with vacuoles, and others are frankly necrotic. Adjacent are still other cells with multiple nuclei and occasionally with mitotic figures. The hepatic cells are not arranged in any definite pattern, and if a central vein is present in a nodule it is likely to be eccentrically

placed. The fibrous tissue is edematous, and the contained vessels are dilated. There is a conspicuous infiltration with lymphocytes, mononuclear cells, and a few polymorphonuclear leukocytes. Small bile ducts are prominent, and points of union between the bile ducts and the hepatic columns are observed.

In the quiescent lesion the nodules are sharply outlined and the hepatic cells show no necrosis, but there may be fatty metamorphosis. The internal arrangement of the cells within a nodule is irregular, and the central veins are characteristically absent. The connective tissue between the nodules is dense and collagenous, and there is only a slight infiltration with lymphocytes. The bile ducts are not prominent.

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LXXVII

Miscellaneous Diseases of the Liver

In addition to lesions related to necrosis and regeneration, and the specific diseases with changes in the liver discussed in many other chapters, there are a few additional notable conditions. The more important are abnormalities of form and position, vascular disturbances, nonparasitic cysts, and tumors.

Abnormalities of Form and Position

Congenital Anomalies. A few examples of abnormal lobulation, accessory lobes, and accessory livers have been described. The most important clinically is an elongation of the right lobe caudally into the lower abdomen—Riedel's lobe (Cullen).

Traumatic Rupture. In newborn infants small capsular hematomas are occasionally observed (Henderson). Less common is rupture of the hepatic parenchyma from strong uterine contractions, from operative delivery, or from too vigorous artificial respiration (Silver). In adults rupture is seen with penetrating wounds, and rarely after nonpenetrating trauma to the abdomen (Shedden and Johnston).

Grooves. Transverse or oblique grooves on the superior surface of the liver—corset liver—have been attributed to pressure from the ribs. In our experience at least some are associated with a fold in the diaphragm.

In Hernias. A part or all of the liver is occasionally found in the sac of a diaphragmatic or umbilical hernia (Jarcho).

Vascular Disturbances

Occlusion of Portal Vein. Complete sudden occlusion of the portal vein as by ligation or by a thrombus incident to operative injury, is almost always followed by death within a short time. The probable explanation is based on the loss of blood into the portal from the systemic circulation of sufficient magnitude to reduce the blood pressure below that compatible with

life (Elman and Cole). In more gradual occlusion of the portal vein, a collateral circulation is established, as in cirrhosis. In some patients the portal hypertension leads to splenic anemia. A definite entity designated cavernomatous transformation of the splenic and portal vein may result from progressive thrombosis and organization (Klemperer).

Occlusion of Hepatic Arteries. Complete occlusion of the main hepatic artery usually leads to massive necrosis of the liver (Andrus, Lord, and Moore). Occlusion of the intrahepatic branches gives a variable result. In some there is no detectable change. In others there is an irregular pyramidal focus of extreme congestion and atrophy of the parenchyma, but no coagulation necrosis—Zahn's infarct. In still others the typical anemic infarct forms.

Thrombosis of Hepatic Veins. Thrombi in the hepatic veins result in congestion and enormous enlargement of the liver. If death does not result, a few patients develop an unexplained polycythemia.

Nonparasitic Cysts of the Liver

There are two general types of nonparasitic cysts of the liver: multiple and solitary (Clagett and Hawkins).

Polycystic Disease of the Liver. In advanced polycystic disease the liver is converted into a mass of small and large cysts with little intervening hepatic parenchyma. A congenital abnormality is probably the cause.

Solitary Cyst. A solitary cyst, if large, is observed in adult life, and is a space-consuming lesion requiring removal. The fluid rarely contains bile (Munroe).

Carcinoma of the Liver

Primary carcinoma of the liver is a common disease in certain peoples in South Africa

and in the Orient, but in Europe and America it is relatively rare.

Pathologic Anatomy. Gross Appearance. The liver is greatly enlarged and weighs from 3000 to 8000 gm. The surface typically has the nodular conformation of cirrhosis, and in addition numerous small and large tumors

portal or hepatic veins. Invasion of the main portal vein, hepatic veins, and inferior vena cava is occasionally seen (Stewart).

Microscopic Appearance. On the basis of histologic structure two types of carcinoma of the liver may be recognized: liver-cell (hepatoma) and bile-duct (cholangioma).

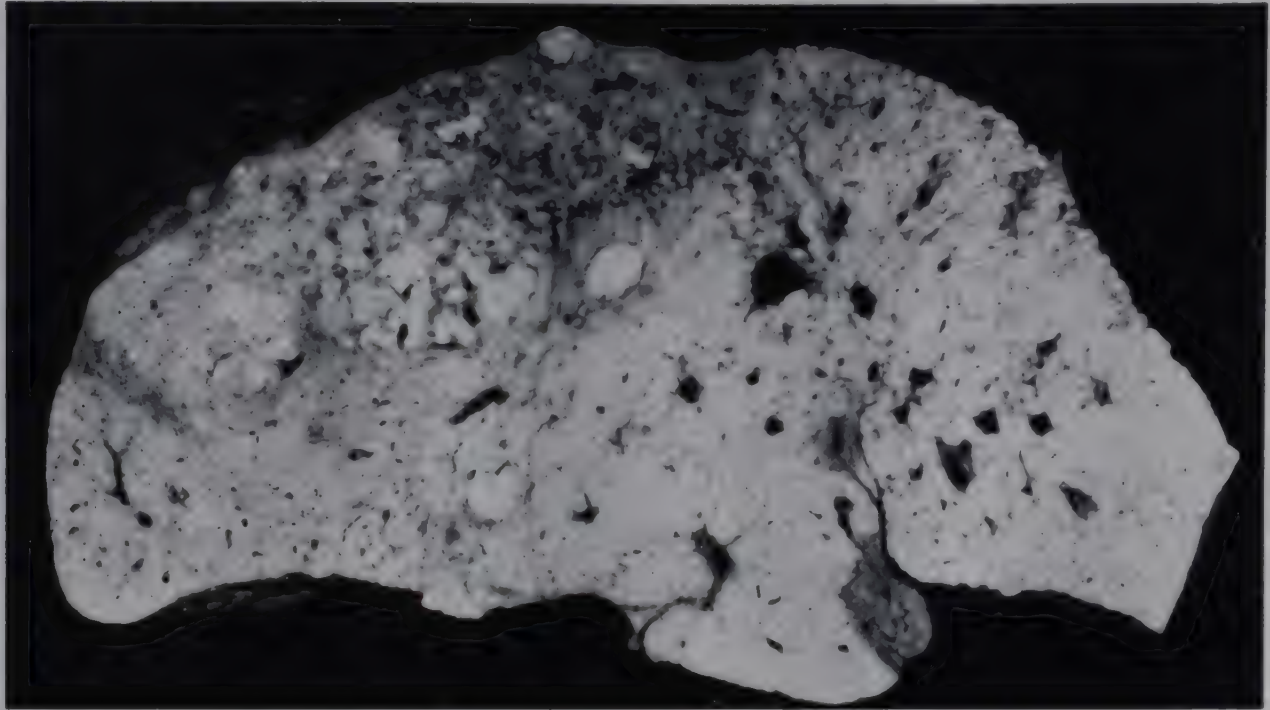


Fig. 299. Primary carcinoma of liver with cirrhosis.

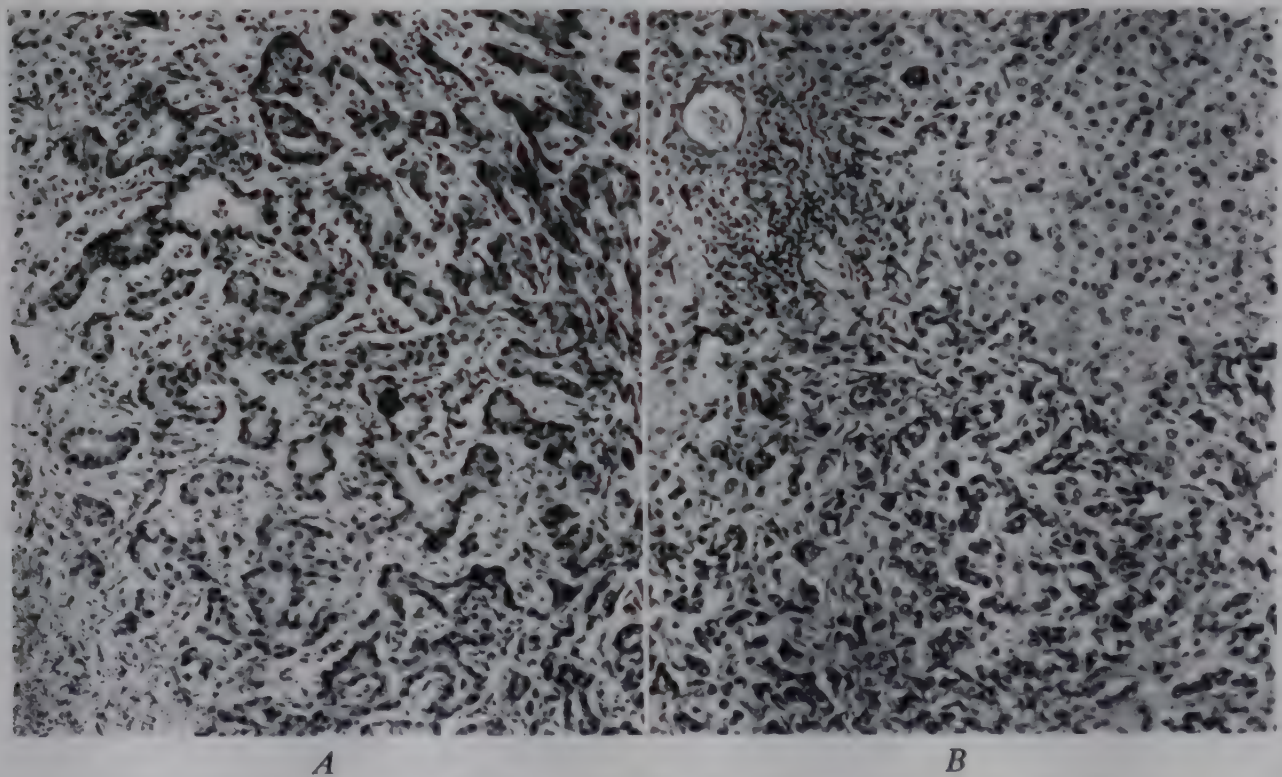


Fig. 300. Carcinoma of liver. *A*, Bile-duct type. *B*, Liver-cell type.

project above the surface. The capsule is slightly thickened, but adhesions are uncommon. On the cut section the double nodulation is readily observed: small, soft nodules of brown hepatic substance—the cirrhosis—and larger multiple tumors, characteristically grayish red, soft, hemorrhagic, and partially necrotic. Some circular nodules are sharply outlined, and careful study will show that they are contained within a branch of the

The liver-cell carcinoma has a trabecular structure in which the columns are solid and lumens sparse. The stroma is scanty and may isolate columns in such a way as to suggest a papillary structure. The cells are pleomorphic, and giant cells and multinucleated cells are common. The cytoplasm is granular and acidophilic, and occasionally contains inspissated bile.

The bile-duct carcinoma is a definite adeno-

carcinoma with an abundant, dense, connective tissue stroma (Winternitz).

Distinguishing Features. In many tumors the distinction between the two types is not clear. The liver-cell type invades the portal vein more frequently. Bile pigment in the liver-cell type is stored within the cells, while

carcinoma of the liver (Bonne). In the Bantus the disease is almost exclusively in men under forty who work in the gold mines of South Africa. In Europe and America the preponderance in men is also evident, but the highest incidence is from forty to sixty years of age. The preponderance of the liver-cell type

TABLE 28. GEOGRAPHICAL DISTRIBUTION OF HEPATIC CARCINOMA

Race or Region	Carcinoma of Liver	
	Per Cent of All Autopsies	Per Cent of All Carcinomas
Bantu (South Africa).....	1.2	37.4
Semi-Bantu (Africa).....	18.7
Oriental races.....	0.85	14.1
European races.....	0.13	1.1
Americans.....	0.25	2.1

in the bile-duct type it is rarely found except in the lumen.

Metastases. Widespread metastases are not common in carcinoma of the liver. The usual sites are the regional nodes, lungs, and tracheobronchial lymph nodes.

Relation to Cirrhosis. From 3 to 6 per cent of all cirrhotic livers also contain primary carcinoma. Approached from the other direction, about 90 per cent of all liver-cell carcinomas and 50 per cent of all bile-duct carcinomas are in livers with cirrhosis. This

in a ratio of 5 or 6:1 holds throughout the world except in children.

Clinicopathologic Correlation. The usually associated cirrhosis and the concomitant hepatic dysfunction have been discussed in a preceding chapter. The space-consuming tumor is responsible for the nodular hepatomegaly and probably for the dull pain. The frequent necrosis in the tumor is the logical cause of the fever and leukocytosis. The duration of life after onset of symptoms rarely exceeds six months (Counseller and McIndoe).

TABLE 29. HEPATIC METABOLISM IN PRESENCE OF BUTTER YELLOW*

	Qo2	Riboflavin (Gammas per Gram Dry Weight)	Co-enzyme I (Gammas per Gram Dry Weight)
Normal diet.....	8.8 (8)	170 (8)	1390 (8)
Basal diet.....	9.0 (14)	124 (12)	1370 (12)
Basal diet and butter yellow.....	9.5 (12)	70 (17)	500 (21)
Basal diet and butter yellow and whole yeast.....	9.0 (8)	170 (8)	1400 (8)
Butter yellow tumor.....	9.5 (8)	33 (8)	150 (8)

* Numbers in parentheses refer to number of animals.

relation is more apparent with diffuse nodular cirrhosis than with any other type.

Incidence. Geographic Distribution. The statistics in Table 28, taken from the many figures published by Berman, show the incidence of carcinoma of the liver. It is clear that there is some racial characteristic, environmental element, or dietary habit of the Bantu natives of South Africa (Gilbert and Gillman; Kennaway), and the Oriental peoples of Japan, China, and Java that leads to

Carcinoma of the Liver in Children. In contrast with the situation in adults, carcinoma of the liver in children is rarely associated with cirrhosis, and the ratio of liver-cell to bile-duct tumors is about 18:1. Most are evident before the end of the second year of life (Steiner).

Experimental Carcinoma of the Liver in Rats. Sasaki and Yoshida demonstrated that rats fed a diet of rice and the dye, *o*-aminoazotoluene, developed carcinoma of the liver.

Soon it was found that the closely related compound, *p*-dimethylaminoazobenzene (butter yellow) is even more effective (Opie). The addition of either whole brewers' yeast or ether extractives of rice-bran or yeast to the diet of the rats completely prevents the formation of tumors (Sugiura and Rhoads). The active principle in the rice-bran and yeast ap-



Fig. 301. Carcinoma of liver with metastases in a rat following ingestion of butter yellow for 345 days. (Photograph by courtesy of Dr. Eugene L. Opie.)

pears to be riboflavin (Kensler, Sugiura, Young, Halter, and Rhoads). The addition of casein to the diet also exerts some protective action, probably through the reducing power of the amino acid, cysteine (Kensler, Sugiura, Young, Halter, and Rhoads). These facts led to an investigation of certain elements of the metabolism of the liver in animals fed butter yellow (Table 29).

It is apparent that the feeding of butter yellow leads to a significant decrease in the values for riboflavin and co-enzyme I in the

liver, and that the tumor tissue is even more deficient in these two elements of normal metabolism. The experiments indicate that phenylenediamine compounds of butter yellow compete with co-enzyme I for some enzyme, probably triosephosphate dehydrogenase (Kensler, Dexter, and Rhoads). It follows that the tumor cells have acquired a new type of metabolism not requiring co-enzyme I, but based on some other enzymatic process foreign to the normal cell. The problem of cure then is to find a chemical which will block this new enzyme system and not affect the normal.

These observations may be related to the classical studies of MacNider on acquired resistance of the liver to hepatotoxic agents. If animals (dogs) recover from a toxic dose of uranium nitrate, they are resistant to a second similar or even larger dose of either uranium or chloroform; and in these animals many of the hepatic cells are of a distinctive metaplastic type. The new cell is capable of performing the hepatic functions, but is resistant to toxic agents. Perhaps the hepatic tumor produced by butter yellow is basically the same process—an attempt by the liver to escape from an injurious agent.

Nodular Hyperplasia of the Liver (Benign Hepatoma). Small, circumscribed but not encapsulated nodules of hyperplastic hepatic tissue, 1 to 5 cm. in diameter, may be found in either cirrhotic or noncirrhotic livers. The cells are arranged in cords and may be singly indistinguishable from the normal. Transitions to an invasive neoplasm are observed, but the relation is not clear (Hoffman).

Cystic Hyperplasia of Bile Ducts. This is a rare lesion in man, but in rabbits yellow, firm or soft nodules of papillary hyperplasia of bile ducts, caused by the protozoon *Coccidium*, are common.

Metastatic Carcinoma of the Liver. The liver is one of the sites of predilection for metastatic carcinoma. Given a metastatic carcinoma of the liver, there is a 26 per cent chance that the primary tumor is in the stomach, 20 per cent that it is in the intestine, 14 per cent that it is in another part of the digestive tract and glands, 14 per cent that it is in the genito-urinary tract, 9 per cent that it is in the upper respiratory tract, and 5 per cent that it is in the lungs (Satterlee).

Carcinogenic Substances in the Liver. Extracts of certain fractions of the human liver

yield a substance that induces the formation of tumors when painted onto the skin or injected into the subcutaneous tissue of mice (Des Ligneris; Steiner). There is some evidence that the agent is more abundant in the liver of patients who have died of cancer than in those free of cancer.

Sarcoma of the Liver

Primary sarcoma of the liver is rare. The more usual types are hemangiosarcoma and spindle cell sarcoma—probably fibrosarcoma. About one-third are associated with cirrhosis.

Sarcoma of the Liver in Rats. In the study of rats for evidence of plague, McCoy noted an intimate association of tumors of the liver and infestation with the tapeworm, *Taenia crassicolis*. Since then many studies have been made of this experimental tumor. The sarcomas originate in the walls of the cyst and are of many cellular types (Dunning, Curtis, and Bullock).

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LXXVIII

Diseases of the Gallbladder and Extrahepatic Ducts

The bile ducts form an extensive system of lumens originating in the bile canaliculi between the hepatic cells, emerging from the liver as the right and left hepatic ducts, and emptying into the duodenum through the major papilla. Most pathologic lesions are of importance because of obstruction.

Congenital Anomalies

The bile ducts form as evaginations of the foregut, and at one stage they constitute solid cords. The cells in the center of these cords undergo degeneration, and a lumen is formed. Congenital anomalies involve lack of formation of this lumen, either diffusely or focally.

Atresia of the Ducts. Variations may in general be placed in the following categories: (1) cases in which there are no demonstrable extrahepatic ducts, (2) cases in which there is atresia of the hepatic ducts, (3) cases in which there is atresia of the common duct, (4) cases in which the gallbladder is represented by a moderate-sized cystic space not connected with the common duct, (5) cases with cystic dilatation of the common duct (McLaughlin), and (6) cases in which the gallbladder connects directly with the duodenum, but in which there are no other extrahepatic ducts. If, as is usual, the child survives for some time, there is the typical picture in the liver of obstructive biliary cirrhosis in all types.

Jaundice usually appears on the second to the third day of life. Some biliary pigments may be found in the stool, probably excreted from the blood by the colon (Ladd).

Anomalies of the Gallbladder. Congenital malformations include absence of the gallbladder, duplication, bifid gallbladder, and diverticula. An abnormal position within the substance of the liver, on the inferior surface,

and on the under surface of the left lobe, and suspension on a mesentery have been reported. A transverse partition in the fundus of the gallbladder produces an anomaly known as "phrygian cap" (Gross).

Effects of Obstruction of the Bile Ducts—Obstructive Biliary Cirrhosis

The term "obstructive biliary cirrhosis" should be reserved for those pathologic changes which occur in the liver as the result of uncomplicated obstruction of the bile ducts, either extrahepatic or intrahepatic. Two general types are recognized: (1) that which occurs in children with congenital atresia or stenosis of the bile ducts, and (2) that which occurs in children or adults with obstruction of the bile ducts by any one of a variety of acquired lesions.

Pathologic Anatomy. With congenital atresia of the bile ducts, the liver is firm but not enlarged. It is dark green, and the surface is finely granular. There is proliferation of the terminal bile ducts, which become lengthened, tortuous, dilated, and filled with inspissated dark-brown bile. In the periportal areas there is proliferation of the connective tissue, which is infiltrated with mononuclear cells. The Kupffer cells are increased, and many contain droplets of inspissated bile.

In acquired obstruction of the bile ducts, the liver is normal in size and contour, and the surface is smooth or at the most slightly granular. The consistency is slightly increased, especially in the advanced cases. The entire organ is dark yellow. The microscopic appearance is similar to that in the congenital variety. Small infarcts are not uncommon (MacMahon and Mallory; Lieber and Stewart; Gibson and Robertson).

Causal Factors. The causes of acquired obstruction of the common bile duct are extremely varied, but two are outstanding—choledocholithiasis and carcinoma of the head of the pancreas. There is a tremendous volumetric increase in the bile ducts and an obliteration of the small normal saccules along the large bile ducts (Judd and Counselor). The cells farthest from the orifice of the bile ducts are usually more deeply pigmented.

In animals ligation of the common bile duct is followed by the typical changes of obstructive biliary cirrhosis: necrosis of the hepatic cells, proliferation of the bile ducts, and peri-

liver and the absence of bile from the gastrointestinal tract, there is hypoprothrombinemia. The retention of the constituents of the bile, particularly the bile acids, leads to parenchymatous damage to many other organs, notably the kidneys, the heart, and the brain. In the skin the retention of bile frequently leads to intense itching (Boyce and McFetridge).

Cholecystitis. Cholangitis

Inflammation of the gallbladder constitutes one of the most common conditions for

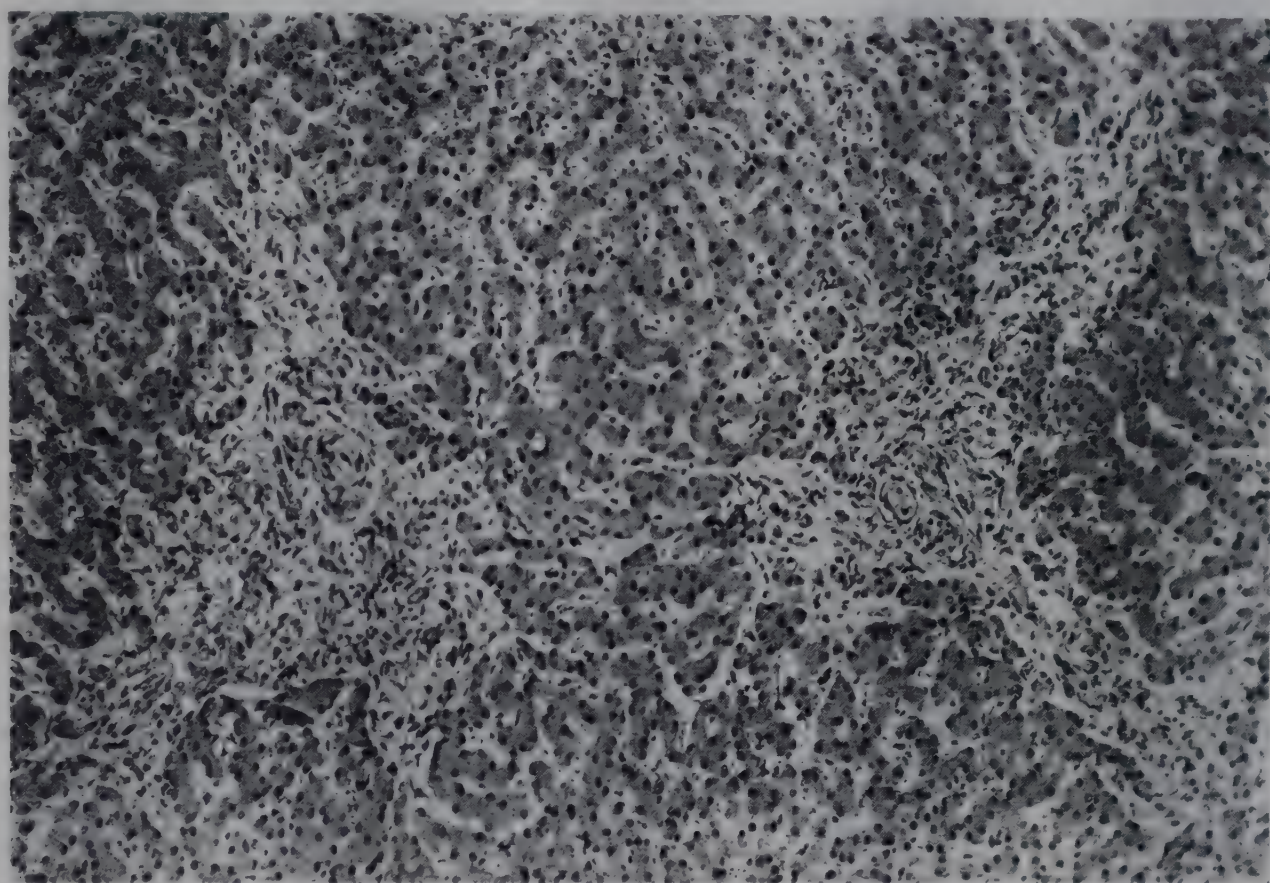


Fig. 302. Obstructive biliary cirrhosis.

portal fibrosis. The necrosis results from dilatation of the bile ducts and retention of the bile, while the fibrosis and proliferation may be produced solely by the dilatation of the bile ducts (Moore, Hellman, and Jacobius).

Clinicopathologic Correlation. Since obstructive biliary cirrhosis is always a lesion secondary to some other disease, only the lesions in the liver can be practically correlated with the clinical findings. The liver is usually not enlarged, although it may be palpable because of depression of the diaphragm. The damage to the liver is reflected in a decrease of functional ability as measured by one of the hepatic function tests (Snell and Magath). Because of the damage to the

which patients seek relief. The distinction between true inflammations and other related conditions is not always clear (Johnson, Malmstrom, and Volk).

Pathologic Anatomy. Two types of cholecystitis are recognized: acute and chronic.

Acute Cholecystitis. The gallbladder is distended, and the wall is thin and tense. Over the peritoneal surface there may be a fine fibrinous exudate. The blood vessels of the wall are prominent. The lumen is filled with a cloudy, bile-stained fluid, varying from a limpid to a thick, viscid pus. The mucosa is intensely hyperemic, and there are frequently small and large ulcers. The epithelium, except in the region of the ulcerations, is intact. All

layers are edematous and infiltrated with polymorphonuclear leukocytes. The lymph nodes about the cystic duct are enlarged and soft, and bulge from the cut surface. The liver is usually slightly enlarged, with mild pericholangitis in all parts.

EMPHYEMA OF THE GALLBLADDER. If suppurative inflammation occurs in a gallbladder, the cystic duct of which is occluded, the lumen fills with a thick pus, and the condition is known as "empyema."

HYDROPS OF THE GALLBLADDER. As the suppurative inflammation subsides, the exudate

lesions as seen with the microscope are obliteration of the plica, fibrosis in the mucosa, partial fibrous replacement of the muscularis, and fibrous thickening of the serosa (Fig. 303). In all layers there is diffuse or focal infiltration with lymphocytes, especially about the nerves—a possible explanation of the pain in chronic cholecystitis (Womack). The lymph nodes about the cystic and common ducts are slightly enlarged and firm. The head of the pancreas is not infrequently enlarged and firm as the result of chronic interstitial pancreatitis.

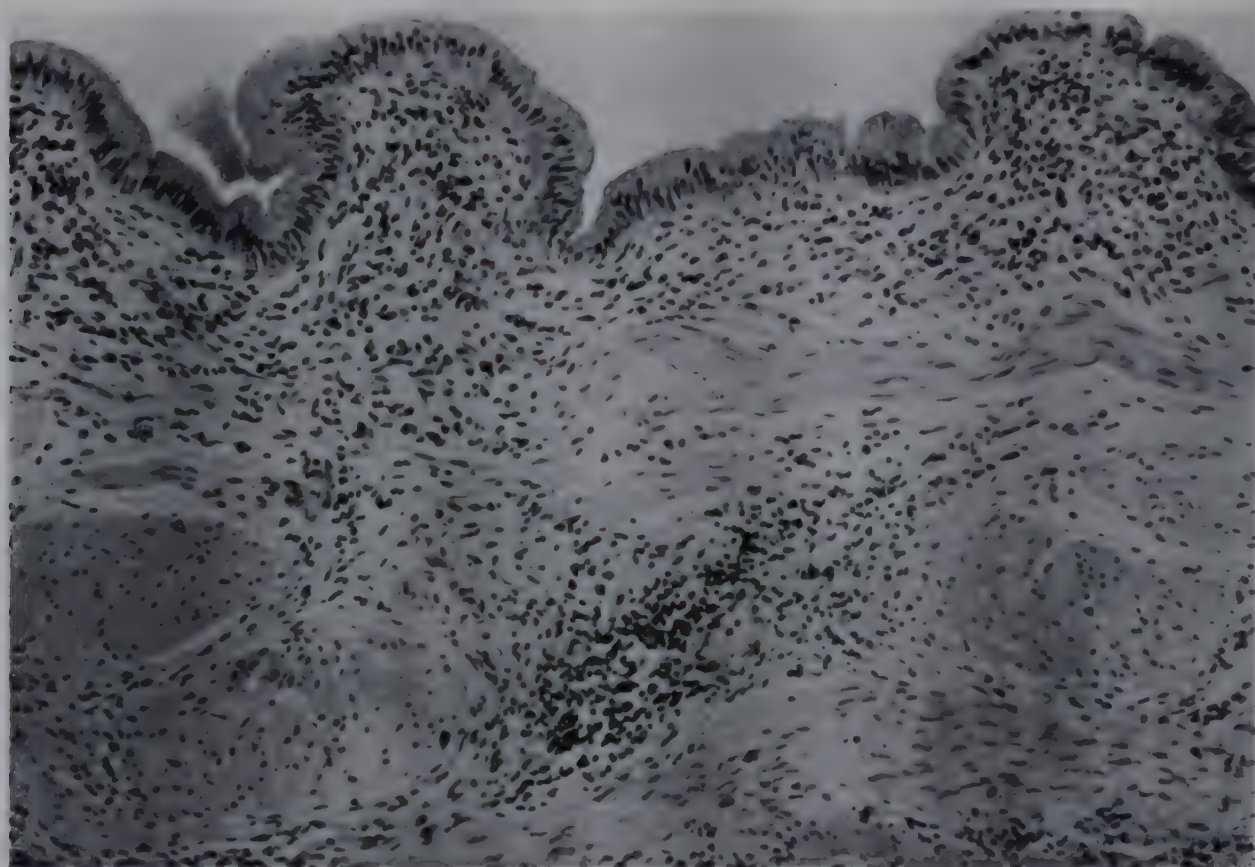


Fig. 303. Chronic cholecystitis. Note absence of plica, cellular infiltration, and separation of bundles of muscle.

within the lumen undergoes autolysis and becomes a thin, colorless fluid. The epithelium regenerates over the surface and secretes mucus into the lumen. The wall is largely replaced by fibrous tissue, and the result is a distended, white, opaque sac, enclosing a colorless, viscid fluid—hydrops of the gallbladder.

Chronic Cholecystitis. The gallbladder varies in size from normal to a small, contracted mass. There are frequently dense adhesions to the duodenum, to the stomach, or to the transverse colon. The wall is thickened and opaque. The mucosal markings are indistinct or obliterated, and fine radiating scars are seen in the mucosa. In the adjacent liver the capsule is thickened and contracted by proliferation of fibrous tissue. The characteristic

Pathogenesis. There are four possible routes for bacteria to reach the gallbladder: through the blood, through the lymph, through the bile ducts from the liver, and through the bile ducts from the duodenum. Undoubtedly, each of these is operative on occasion, but most evidence indicates that the lymphogenous pathway is the commonest.

Bacterial Causes. Some investigators have found mostly streptococci in acute and in chronic cholecystitis and others mostly colon bacilli. The work of Wilkie appears to reconcile these two conflicting observations. He found that cultures of the wall and of the cystic lymph node gave only streptococci which were inhibited in growth by bile. In the lumen were colon bacilli not inhibited by bile. The logical conclusion is that the colon bacilli

are secondary invaders in the lumen, and not the cause of the mural lesions.

Cholangitis. Since the gallbladder and ducts constitute a single anatomic intercommunicating unit, infection of the gallbladder usually accompanies infection of the ducts, and vice versa. In acute cholangitis the ducts are dilated and filled with thick, bile-stained pus. The wall is edematous and infiltrated with leukocytes. As the infection subsides there is proliferation of fibrous tissue both in the ducts and in the periductal tissues, with resulting fibrosis. In most cases there is some form of obstruction—calculi, inspissated bile, or pressure from surrounding tumors (Klemperer).

Cholangitic Abscesses. Occasionally, in association with suppurative cholangitis there are abscesses in the liver. Uniformly distributed throughout an enlarged, soft liver are cavities 1 to 10 mm. in diameter, filled with bile-stained pus. Occasionally, a peripheral abscess ruptures, and peritonitis or a subphrenic abscess follows:

Cholesterolosis of the Gallbladder. Both in otherwise normal and in pathologic gallbladders small, bright yellow flecks, 1 mm. in diameter, may be deposited in the crests of the plicae. Collections of foam cells just beneath the epithelium, and occasionally fusiform crystals, are seen microscopically. This condition probably represents a disturbance in the metabolism of cholesterol (Lewis and Peterson).

Effects of Cholecystectomy. Most patients with cholelithiasis are relieved by cholecystectomy, but only about 80 per cent with cholecystitis alone get permanent relief, probably because of persistence of the infection in the adjacent tissues, in the liver, and in the ducts. Study of the ducts many years after cholecystectomy shows slight dilatation and the presence of numerous small diverticula—the former parietal saccules (Counseller and McBride).

Cholelithiasis

Pathologic Anatomy. On the basis of chemical composition and physical structure there are three basic types of gallstones: solitary cholesterol stone, calcium pigment stone, and a concentrically laminated faceted stone. The barrel stone is a modification of the faceted stone, and the combination stones are

composed of successive layers of two of the three basic types. Finally the stones formed in the common duct are modified calcium pigment stones (Aschoff).

Solitary Cholesterol Stone. This is typically a single, spheroidal stone with a longest diameter of 1 to 2 cm. and a shortest diameter of about 1 cm. It is coarsely nodular and translucent bluish white. On fracture through the center, large flat crystals or flakes are seen. On chemical analysis about 99 per cent of the dry weight is cholesterol.

Calcium Pigment Stone. These are small, dark-brown, firm stones, 2 to 5 mm. in diameter, and 4 to 10 in number. The surface is irregular. There are frequently multiple prominent points projecting from a stone. The principal chemical component is calcium bilirubinate, with smaller amounts of cholesterol and protein.

Concentrically Laminated Faceted Stones. This is the typical gallstone, found in numbers varying from 5 to 300. Each stone is white or greenish white, and the surface is composed of multiple, irregular facets, with rounded edges and corners. On a fractured surface two parts are discernible: a central nidus of pigment and frequently a drop of fluid. About the nidus there are concentrically arranged laminae, some light in color, others dark, some thin, and some thick. There is no crystalline structure except for a few small crystals near the center. In general the faceted stones within any one gallbladder are of one size, or of several sizes representing successive crops.

Barrel Stones. Typical barrel stones are two in number. The diameter is the same as that of the lumen of the gallbladder, and the two are faceted to one another on one surface only. The gallbladder is usually contracted and fibrous, and forms a tight encapsulation about the stones. The fractured surface has the same concentrically laminated appearance as in the fully faceted stones.

Combination Stones. Not infrequently in a gallbladder with many faceted stones there is one spheroidal larger stone. The fractured surface consists of two distinct parts—a central part up to 15 mm. in the longest diameter, identical with the solitary cholesterol stone, and a peripheral part identical with the concentric laminae of the faceted or barrel stone. It is assumed that the solitary cholesterol

stone was formed first, and later covered by another type of material—hence the name “combination stone.” There are similar com-

bination stone, a typical faceted calculus in the center and a peripheral layer of material deposited in the common duct.



Fig. 304. 1 and 3, Cut section of combination stones. 2, 5, 6, 7, 8, 9, and 11, Faceted stones. 4, Barrel stones. 10, Pure cholesterol stone. 12, 13, 14, and 15, Calcium pigment stones.

bination stones formed from the calcium pigment stone and the laminated stones.

Stones in the Extrahepatic Ducts. Stones formed in the extrahepatic ducts lack the density and firmness of stones formed in the gallbladder. They are rusty red or jade-green, and crumble on the slightest pressure. Occasionally, a stone in the common bile duct is a com-

Intramural Stones. Soft or hard stones may be formed in the Luschka's crypts of the wall of the gallbladder (Robertson and Ferguson).

Relation to Cholecystitis. By and large the solitary cholesterol stone and the calcium pigment stone are found in gallbladders that are not otherwise diseased. Faceted stones, barrel stones, and combination stones are rarely

found in gallbladders that are not the seat of acute or chronic cholecystitis. It is not possible to determine whether the stones are the cause or the effect of the inflammation.

Incidence. The incidence of cholelithiasis varies in different parts of the world. Average figures for those over twenty years of age are:

at autopsy have not produced symptoms unless it is assumed that obscure digestive ailments are related to them. Cholelithiasis in children is not common.

Causal Factors and Pathogenesis. Despite the most exhaustive investigations, the cause of gallstones remains an enigma. Logically

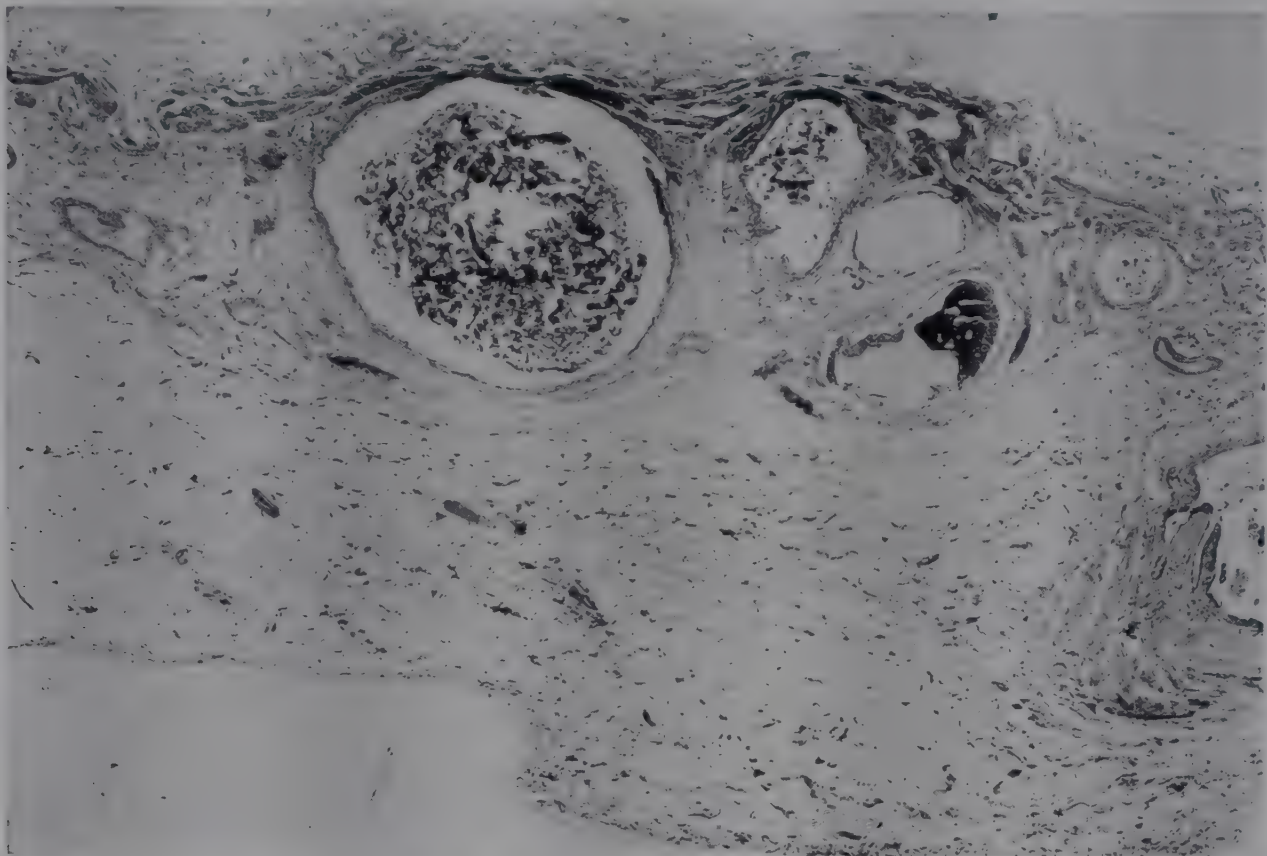


Fig. 305. Intramural gallstones.

western Europe, 10 per cent; Russia, 2.2 per cent; Bosnia, 1.9 per cent; England, 7 per cent; India, 5.4 per cent; China, 2.2 per cent; Japan, 5 per cent; and the United States, 6

TABLE 30. INFLUENCE OF AGE AND SEX ON INCIDENCE OF CHOLELITHIASIS

Age	Per Cent with Cholelithiasis	
	Male	Female
21-30.....	0	5
31-40.....	1.45	11.51
41-50.....	4.24	21.90
51-60.....	6.75	17.07
61-70.....	11.20	29.03
Above 70.....	13.90	24.44

per cent. The influence of age and sex is shown in statistics on white persons at the Cook County Hospital, Chicago (Table 30).

The incidence in Negroes is lower than in whites (Jaffe). Most of the gallstones found

there are two possibilities: (1) changes in the composition of hepatic bile because of aberrations of general metabolism or disease of the liver, and (2) changes in the gallbladder favoring the formation of stones.

Observations favoring *hepatic origin* are the high incidence of calcium pigment stones in hemolytic jaundice, in which there is excessive excretion of pigment (Giffin); the high incidence of solitary cholesterol and combination stones in women, and more particularly in multiparous women in whom repeated disturbances in cholesterol metabolism may be assumed (Robertson); and the fact that the bile salts, especially desoxycholate, are known to hold the cholesterol in solution.

Observations favoring a *cholecystic origin* are the close association of multiple faceted stones with inflammation of the gallbladder; the known rapid absorption of bile salts by an inflamed gallbladder; the high concentration of cholesterol in gallbladder bile as compared to hepatic bile, indicating an absorption of fluid, and concentration leading to

alterations of the cholesterol-bile-salt ratio (at a ratio of less than 18:1 cholesterol precipitates); the recovery of bacteria from the centers of gallstones; and the fact that there is stasis of bile in the gallbladder, and that throughout all hollow viscera stasis leads to the formation of calculi.

It must be realized that in studies on man the gallstones may have been deposited years before, and that the causal factors may not be demonstrable at the time of examination. It is probable that one or more of the many factors are operative in any given instance, and that there is no one cause of cholelithiasis.

Stricture of the Ducts. The usual causes of fibrous stricture of the bile ducts with stenosis are ulceration from an impacted stone and injury during a surgical procedure. The most frequent site is at the junction of the cystic and hepatic ducts (Cattell).

Biliary Fistulas. External. The most common external fistulous communication of the gallbladder is to the surface of the body about the umbilicus, or in the right upper quadrant of the abdomen. If the cystic duct is open, a pigmented bile issues from the tract; but if the cystic duct is occluded there is discharge of a viscid, colorless mucus—mucous fistula (Hicken, White, and Coray).

Internal. The more common fistulas between the biliary tract and the internal hollow viscera are from the gallbladder to the duodenum, stomach, and transverse colon, and from the common bile duct to the duodenum. The most frequently observed is the cholecystoduodenal type (Puestow).

Pathogenesis. Except for those following cholecystostomy and usually associated with obstructions of the common bile duct, most fistulas result from proliferation of an ulcer through the wall of the gallbladder or common duct into an adjacent viscus. The initial lesion is probably a decubital ulcer due to pressure by a stone. The bronchobiliary fistula is based on rupture of an abscess of the liver through the diaphragm and into a bronchus.

Clinicopathologic Correlation. In external fistulas the diversion of bile leads to improper digestion and absorption of fat and the fat-soluble vitamins. In internal fistulas the unguarded opening of the intestinal tract into the biliary system allows intestinal bacteria to enter the ducts, and the complications of cholangitis and cholangitic abscesses are the usual

termination. Stones discharged into the intestine through a fistula may cause intestinal obstruction.

Carcinoma of the Gallbladder

Pathologic Anatomy. Carcinoma of the gallbladder may be divided into three types, papillary carcinoma, infiltrating carcinoma, and mucinous carcinoma. The papillary carcinoma is a papillary fungating mass in the lumen of the gallbladder. The wall is slightly thickened, but there is little invasion of the wall of the gallbladder or of the adjacent liver. The infiltrating carcinoma is an indefinitely lobulated, firm mass in the wall of the gallbladder, usually with ulceration of the mucosa over it. In most tumors of this type there is a mass of similar tissue in the parenchyma of the liver, directly adjacent to the gallbladder. The mucinous carcinoma is a large, bulky tumor partially filling the lumen of the gallbladder, composed largely of characteristic bluish gray, translucent mucin. Most carcinomas of the gallbladder are adenocarcinomas, but a small percentage are carcinoma simplex, and there is a rare instance of epidermoid carcinoma (Arminski).

Incidence. Carcinoma of the gallbladder constitutes from 1 to 2 per cent of all carcinomas in men, and from 6 to 10 per cent in women. The sex ratio is about 1:4. It is rarely observed before the age of forty, and the average age is sixty years.

Causal Factors. Gallstones are present in about 90 per cent of all cases of carcinoma of the gallbladder. In all gallbladders containing stones associated carcinoma is found in about 5 per cent. These two statements leave no doubt that carcinoma of the gallbladder is definitely related to cholelithiasis (Mohardt). The exact mechanism is not, however, entirely understood.

Clinicopathologic Correlation. Most patients have histories that are more readily accounted for on the basis of associated cholelithiasis than on the basis of carcinoma. Symptoms directly referable to the tumor are probably limited to pain from invasion of the lymphatics about nerves and jaundice from pressure on the common bile duct by lymph nodes filled with metastases.

Sarcoma of the Gallbladder. Benign tumors (Shepard, Walters, and Dockerty) and

sarcoma of the gallbladder are extremely rare. The usual type is either fibrosarcoma or leiomyosarcoma.

Carcinoma of the Extrahepatic Ducts

Pathologic Anatomy. The most common site of carcinoma of the extrahepatic ducts is either at the junction of the cystic, hepatic, and common ducts, or in the common duct itself. The tumors are usually small, rarely over 1 cm. in diameter, and they form a firm, grayish white mass, replacing both the wall and the lumen of the ducts. If there is complete occlusion of the hepatic duct, the biliary system above will be greatly dilated and filled with a colorless, thick, tenacious fluid known as "white bile." If the occlusion is in the common duct, the system above will be moderately dilated and filled with a dark-green or black tenacious fluid, known as "black bile." Most of the tumors are adenocarcinoma or carcinoma simplex.

Clinicopathologic Correlation. In striking contrast with carcinoma of the gallbladder, ductal carcinoma occurs about equally in the two sexes, or is perhaps slightly more frequent in men. The average age is about sixty years. Nothing is known concerning causal factors. It is evident from the position of the tumor that jaundice is the commonest and earliest sign. Pain is caused by invasion of the perineurial lymphatics. Ascites may be caused by peritoneal implants, by obstruction of the portal vein from enlarged lymph nodes, or by cirrhosis of the liver (Kirshbaum and Kozoll).

Other Tumors of the Extrahepatic Ducts. Other tumors—papilloma, fibroma, leiomyoma, and sarcoma—of the extrahepatic ducts are uncommon (Chu). The rare congenital cyst of the common duct produces the same clinical syndrome of obstruction (Shallow, Eger, and Wagner).

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LXXIX

Diseases of the Pancreas

The pancreas is in reality a double organ consisting of secretory acini and the islands of Langerhans. Only the former will be discussed in this chapter. The islands are an endocrine organ, and lesions of them will be considered in Chapter XCVIII, p. 867.

Congenital Anomalies. The pancreas is formed from two diverticula of the entoderm arising on opposite sides of the duodenum. Failure of migration of the ventral anlage is responsible for the "annular pancreas" which causes stenosis of the duodenum (Gross and Chisholm). Failure of fusion of the ducts and anlagen is occasionally seen.

The most common anomaly is the accessory pancreas in the wall of the stomach and small intestine. It is a firm, grayish yellow nodule in the submucosa, consisting of ducts, acini, and islands (Moore). The adenomyoma of the stomach is probably derived from accessory pancreatic tissue in which only ducts and stroma develop.

Acute Interstitial Pancreatitis

Until 1930 acute conditions of the pancreas were considered to be rare and highly fatal. After the development and use of the test for serum amylase it was realized that a number of patients with acute symptoms and signs pointing to the abdomen had elevated serum amylase values and disease of the pancreas (Elman).

Pathologic Anatomy. The pancreas is enlarged and firm, especially in the head. It is edematous and whiter than normal, and small foci of fat necrosis are present. The interstitial tissue is edematous and infiltrated with polymorphonuclear leukocytes. The blood vessels are dilated. A colorless or brown fluid exudes from the lesser peritoneal sac.

Clinicopathologic Correlation. Acute interstitial pancreatitis is observed largely in young

adults of both sexes. The inflammation reaching the peritoneum causes the usual signs and symptoms: pain, nausea and vomiting, local tenderness, and spasm of the muscle. The serum amylase value characteristically returns to normal by the second to the sixth day. Recurrence is the rule, and small foci of older fat necrosis may be visible. The mortality is low, and recovery takes place in one to two weeks.

A specific type of interstitial pancreatitis occurs in mumps, and less commonly in the other infectious diseases. The pathologic changes in all types of acute interstitial pancreatitis shade into acute necrosis of the pancreas, but the differences in the course and mortality are sharp.

Chronic Pancreatitis. It seems probable that most reported cases of this condition are the fibrosis secondary to arterial disease. One exception is the induration of the head of the pancreas seen in patients with chronic cholecystitis.

Calcification in the Pancreas. The rare occurrence of intrapancreatic calcification is probably the result of chronic inflammation or of a mild pancreatic necrosis (King and Waghelstein).

Acute Necrosis of the Pancreas

Modern concepts of acute necrosis of the pancreas date from two publications, the first by Reginald Fitz in 1889, summarizing the clinical manifestations, and the second by Eugene L. Opie in 1903, reporting the demonstration of a stone in the ampulla as a possible cause.

Types. Three types of acute necrosis of the pancreas are recognized: hemorrhagic, gangrenous, and suppurative.

Pathologic Anatomy. A part or all of the pancreas is converted into a soft, diffuent,

gray-red or dark-red mass. Early, the limits of the necrosis are not sharply outlined, and the adjacent tissue is edematous, red, and indurated. In late stages a sequestrum is distinct. The interstitial tissue is edematous and filled with extravasated red blood cells. There is little infiltration with white cells except in the suppurative type. The blood vessels, especially the arteries, show necrosis of the wall, and the lumens are occasionally filled with thrombi. In the surrounding peripancreatic fat tissue there are foci of fat necrosis.

action of the regurgitated bile salts, but the bile and the pancreatic ducts are not arranged to make this anatomically possible in all cases.

In summary, it seems probable that acute necrosis of the pancreas may result from any one of the variety of causes, and that different factors are at work in different cases (Lewison; Jones).

Pathogenesis. After active enzyme is liberated into the interstitial tissue, there is digestion. If the tryptic activity is high, necrosis of the walls of vessels results in hemorrhage;

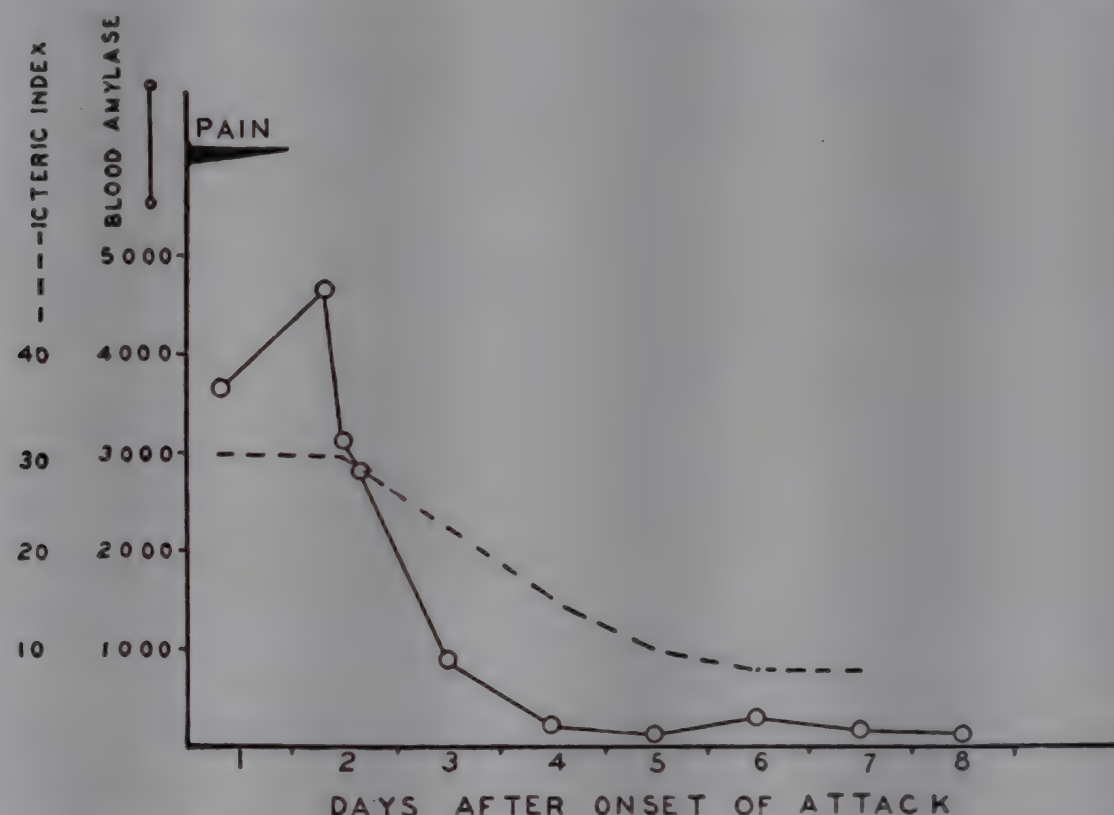


Fig. 306. Serum amylase and icteric index in acute interstitial pancreatitis. (By courtesy of Dr. Robert Elman.)

Causal Factors. The immediate precipitating cause of acute necrosis of the pancreas is liberation of pancreatic juice into the interstitial tissue. It is further probable that the ductal rupture is the result of a temporary increase of pressure. This may be caused by impaction of a gallstone in the ampulla, by spasm of the sphincter of Oddi, by edema of the tissues of the major papilla as in acute duodenitis, by metaplasia of the epithelium of the smaller pancreatic ducts, or by inspissation of secretion in the ducts. The frequent occurrence in alcoholics, and the sudden onset after a meal, may be explained by the stimulating effects on pancreatic secretion. The known common association with cholecystitis with or without stones is taken as evidence that lymphatic drainage of the infection is a cause. Some believe that the necrosis is attributable to the toxic and cytolytic

and if lipase activity is high, fat necrosis is prominent (Rich and Duff).

Clinicopathologic Correlation. Acute necrosis of the pancreas occurs more frequently in women than in men (2:1) in middle adult life. The irritation of the peritoneum is extreme and of sudden onset, hence the commanding intra-abdominal symptoms: pain, nausea, and rigidity. The serum amylase value is early increased, but rapidly returns to normal. Diabetes is rarely a complication. The usual course is three to ten days. The mortality is about 30 per cent, even with early adequate surgical treatment.

Hemorrhage into the Pancreas. Occasionally an artery or an aneurysm ruptures into the pancreas—apoplexy of the pancreas. Acute hemorrhagic necrosis may follow, or the hemorrhage may resolve and a cyst be formed.

General Effects of Obstruction of the Pancreatic Duct

Pathologic Anatomy. The general effects of obstruction of the pancreatic duct are the

Effects of Pressure in Ductal System. The obstruction of the duct leads to the accumulation of fluid in the entire ductal system under increased pressure. The fluid is composed in part of mucus secreted by the ductal epith-



Fig. 307. Gallstone impacted in ampulla in association with acute hemorrhagic necrosis of the pancreas.

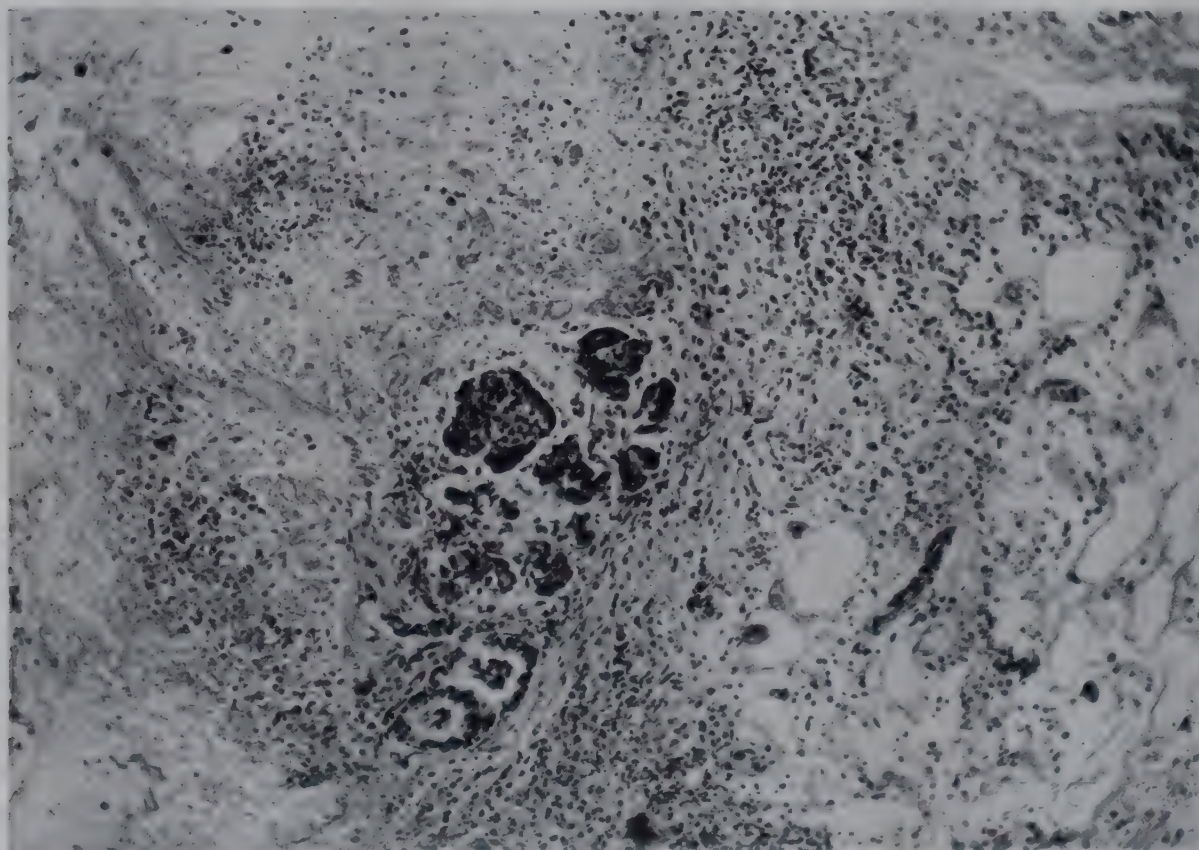


Fig. 308. Acute hemorrhagic necrosis of the pancreas.

result of one or both of two factors: pressure on the pancreas, and the absence of the pancreatic secretion in the lumen of the intestine.

elium, and in part of the specific secretion of the acinic cells. The acinic tissue of the pancreas undergoes gradual atrophy and disap-

pearance, so that the pancreas is small, firm, and fibrotic (Fig. 309). The ductal system is dilated, and the parenchyma is composed of firm, fibrillar tissue, with little evidence of the yellow or grayish yellow lobular architecture of the pancreatic parenchyma. Numerous small and large ducts and islands of Langerhans are embedded in a collagenous stroma (MacCallum). If there is associated inflammation, the islands of Langerhans may also be destroyed, and there will be diabetes.

Effects of Absence of Pancreatic Secretion. The loss of secretion from the gastro-intes-

iciency" (Dragstedt; Norris, Beard, and Gerber). The subject is fully discussed in Chapter XCVIII, p. 871.

Pancreatic Calculi

Pancreatic calculi are usually found in the larger ducts, and are white or grayish white, spherical or irregular bodies. They are composed largely of calcium carbonate, but small amounts of calcium phosphate, magnesium carbonate, fibrin, and cholesterol may be present. If the calculi completely or partially oc-

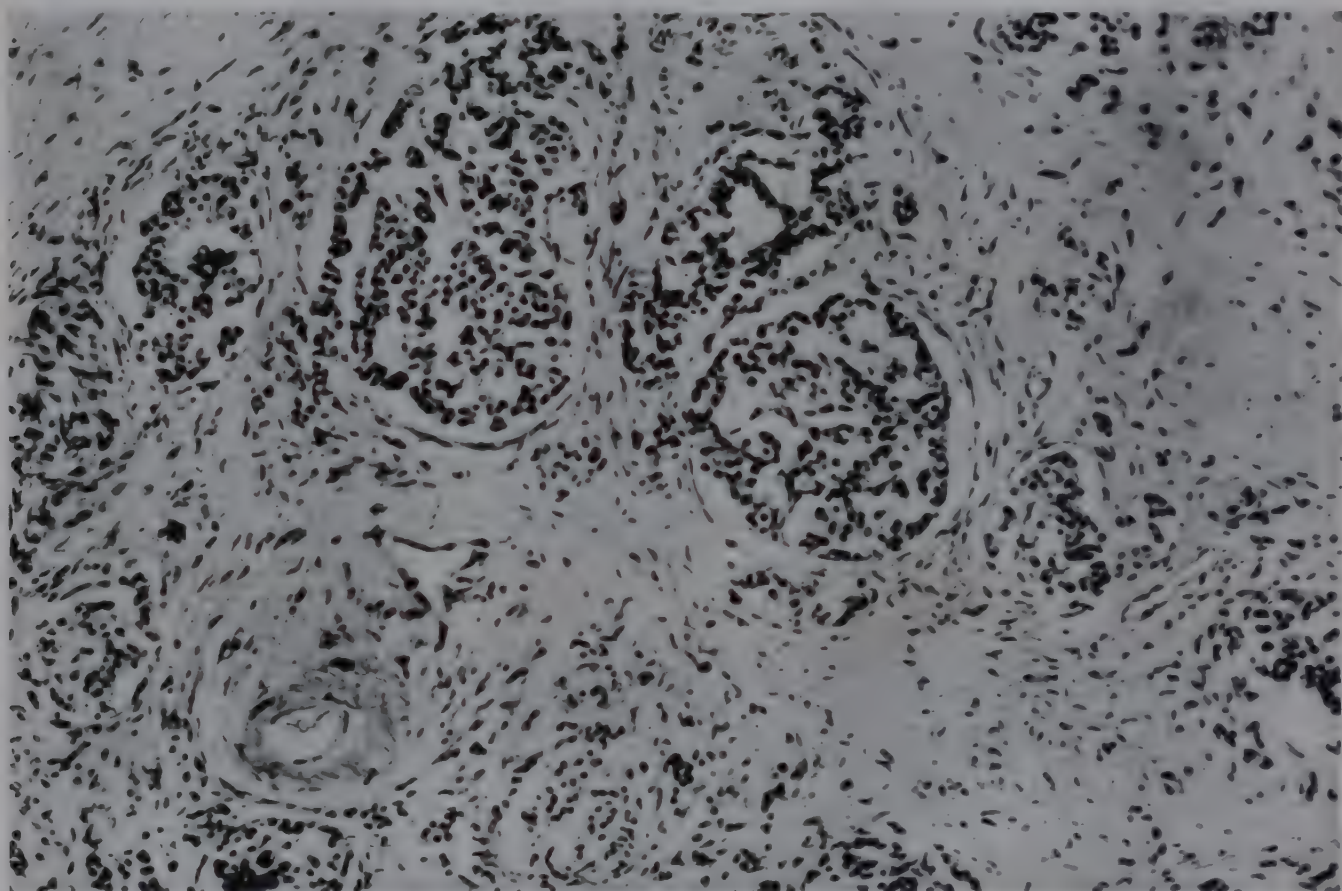


Fig. 309. Atrophy of the pancreatic acini in obstruction of the duct.

tinal tract is of greater clinical importance. There is inadequate digestion of fats and consequent steatorrhea. Typically the stools are pale, large, and bulky. In adults, chemical analysis of the stools for fat may be necessary to establish the diagnosis, as the gross appearance is not characteristic. Studies of the blood amylase indicate that early in ductal obstruction of the pancreas there is resorption of large amounts of amylase into the blood, but that with atrophy of the acinar tissues there is a fall of the amylase value to below normal (Elman, Arneson, and Graham).

Lipocaic Deficiency. There is some suggestion that the acini of the pancreas secrete into the blood stream a substance in the absence of which fatty degeneration of the liver develops, a condition known as "lipocaic de-

clude the ducts, as they usually do, the ducts distal to the point of occlusion are dilated and thin-walled. The pancreatic parenchyma is atrophic, and consists of only ducts and islands. Occasionally, secondary pancreatitis brings about destruction of the islands also. Under these conditions there is, in addition to pain and steatorrhea from occlusion of the ducts, diabetes from the absence of insular tissue. Pancreatic calculi are commonest in the fifth decade, and occur twice as frequently in men as in women (Edmondson, Bullock, and Mehl; Haggard and Kirtley).

Cysts of the Pancreas

True cysts of the pancreas may be defined as cavities within the substance of the organ,

lined by epithelium, and filled with fluid. Accumulations of partially digested pancreatic tissue and blood following trauma and acute hemorrhagic necrosis of the pancreas should be called "pseudocysts" (Pinkham).

Cysts in general may be divided into three types: congenital, retention, and neoplastic. *Congenital cysts* of the pancreas are infrequently a part of polycystic disease involving the kidneys, liver, and lungs (Norris and Tyson). The cavities are smooth-walled, filled with a clear fluid, and lined by a low columnar or cuboidal epithelium, similar to that in the ducts (Rumler). *Retention cysts* of the pancreas represent nothing more than local dilatation of the ducts as the result of obstruction. The best example is cystic fibrosis of the pan-

creas in the pancreas forms a firm, at times nodular, mass. Tumors in the tail of the pancreas are likely to conform to the normal shape and contour of the organ. Most tumors are scirrhous, and are therefore extremely firm and fibrous in appearance, with only an occasional small, yellow island of softer tissue that can be identified. Histologically, there are two general types of carcinoma of the pancreas, designated as "columnar cell carcinoma" and "acinic cell carcinoma." The cells of the columnar cell carcinoma are tall and pale, and are arranged in general in an acinic structure. The nuclei vary in size and shape, but are usually small and highly chromatic. In the acinic cell type, the cells possess a dark-staining cytoplasm similar to that of the nor-

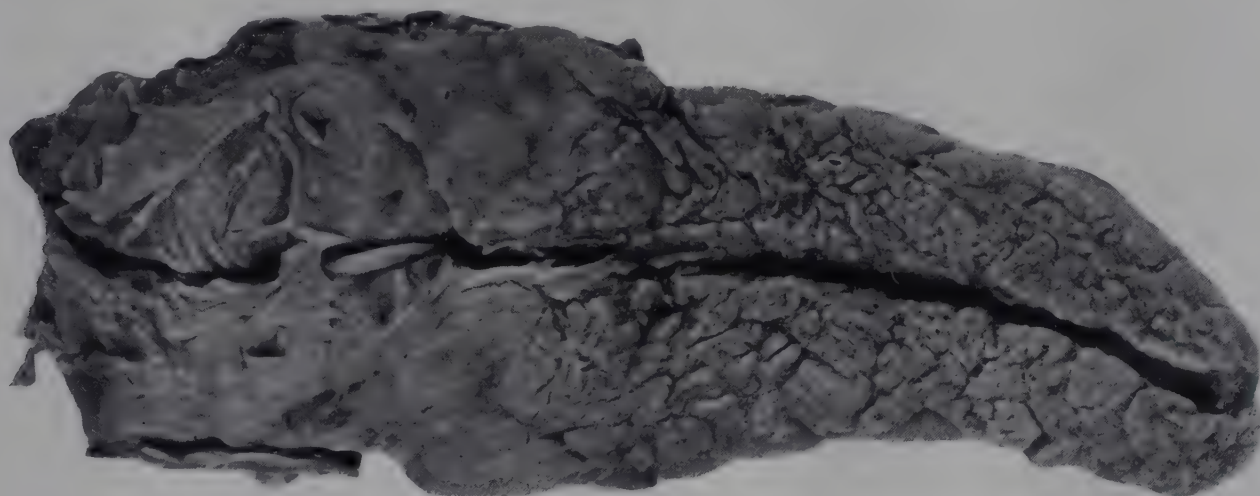


Fig. 310. Carcinoma of the head of the pancreas.

creas (Andersen). *Neoplastic proliferation* of the ductal epithelium, with the formation of cystic spaces into which papillae project, is rare (Rumler; Haban).

Carcinoma of the Pancreas

Carcinoma of the pancreas may be divided into two types: carcinoma of the head of the pancreas, and carcinoma of the body and tail of the pancreas. The latter is about one-third as frequent as the former. The clinical signs and symptoms are different, largely because of the anatomic proximity of other structures that become involved in the neoplastic process. From the standpoint of pathology, the two conditions are entirely similar, except as regards invasion and metastases. A third type of tumor, derived from the islands of Langerhans, will be discussed in Chapter XCVIII.

Pathologic Anatomy. The primary growth

mal acinic cell. The nuclei are placed irregularly throughout the cytoplasm, and there is little gland formation. The cells are arranged in irregular columns and cords without orientation. The columnar cell type is by far the commonest. There is no difference in prognosis in the two types (Duff; Kiefer).

Histogenesis. There is no accurate information available on histogenesis, but because of the similarity of the normal to the neoplastic cells it is assumed that columnar cell carcinoma arises from the ductal epithelium, and that acinic cell carcinoma arises from the secretory cells of the acini.

Invasion and Metastases. In carcinoma of the head of the pancreas the tumor is largely confined to the pancreas and the adjacent duodenum, and surrounds and compresses the common bile duct. Occasionally, the tumor ulcerates into the duodenum. Only a small part of the head is in contact with the peritoneum, and invasion of this structure is,

therefore, unusual. The body and tail of the pancreas, however, are in intimate contact with a number of important structures: the left adrenal gland, the left kidney, and the spleen. Further, the greater part is covered by peritoneum, and direct spread of the tumor cells onto the peritoneum of either the lesser or the greater sac occurs readily and frequently. The lymph nodes along the splenic artery and about the aorta are early involved. Tumor cells in the peritoneum may permeate the diaphragm and involve the pleura or pericardium. The difference in the distant metastases of the two types is well shown in Table 31 from the investigation of Duff. Sixteen cases are included in each of the two categories.

TABLE 31. FREQUENCY OF INVOLVEMENT OF VARIOUS ORGANS AND TISSUES IN CARCINOMA OF THE PANCREAS

Organs and Tissues	Carcinoma of Body or Tail of Pancreas	Carcinoma of Head of Pancreas
Liver.....	13	9
Abdominal lymph nodes.....	10	9
Peritoneum.....	12	2
Lung.....	6	2
Pleura.....	6	0
Diaphragm.....	5	0
Adrenal.....	4	1
Kidney.....	3	0
Vertebra.....	3	0

In tumors of the body of the pancreas, invasion and thrombosis of the splenic vein is not uncommon.

Incidence. Carcinoma of the pancreas is commonest in the sixth decade, but may occur at any age (Kiefer). It constitutes from 1 to 2 per cent of all malignant tumors. Several cases have been reported in children (Mielcarek). It is commoner in men than in women in a ratio of about 3:1.

Causal Factors. The cause of carcinoma of the pancreas is entirely unknown. It has been assumed that a preceding chronic fibrous pancreatitis bears the same relation to carcinoma of the pancreas that cirrhosis of the liver bears to carcinoma of the liver. There is, however, no objective evidence for this assumption, except that carcinoma of the pancreas is commoner in diabetics than in nondiabetics (Marble).

Clinicopathologic Correlation. Practically the only sign or symptom that the two types

have in common is the presence of a mass in the abdomen. In carcinoma of the head of the pancreas, the invasion and obstruction of the common bile duct is responsible for most of the signs and symptoms, discussed under "Obstructive Biliary Cirrhosis," p. 620 (Kaplan and Angrist). In carcinoma of the body and tail of the pancreas the symptoms are again largely dependent on the secondary invasion by the tumor. Growth along the penineural lymphatic spaces is probably responsible for the most common symptom, pain (Drapiewski). Invasion of the peritoneum, together with the formation of multiple emboli in the radicles of the portal vein, produces the ascites. Invasion and thrombosis of the splenic vein lead to enlargement of the spleen. Both

of these may induce varicosity of the esophageal veins, with rupture and hematemesis. Invasion of the left kidney and ureter may give rise to symptoms referable to the urinary tract. There is frequently a decreased carbohydrate tolerance (Levy and Lichtman), but seldom actual diabetes. The absence of pancreatic secretion leads to steatorrhea (Bourne); and the absorption of pancreatic secretions from dilated ducts before atrophy ensues brings about an increase in the blood amylase value (Elman, Arneson, and Graham). The presence of a tumor mass in the head of the pancreas may result in a widening of the curve of the duodenum on roentgenographic examination (Carty). Of particular interest in the field of general pathology is the high association of carcinoma of the body and tail of the pancreas with multiple venous thromboses—31.3 per cent in the series collected by Sproul. This is the only type of carcinoma in which there is this asso-

ciation, and no adequate explanation has yet been offered for it (Kenney).

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LXXX

Diseases of the Buccal Cavity and Esophagus

Carcinoma of the Lip

Pathologic Anatomy. Carcinoma of the lip first appears as a small fissure, which does not heal, near the mucocutaneous junction. In a few instances a tumor forms beneath the skin and there is no change in the epithelium except for slight desquamation. Later, each of

When patients with carcinoma of the lip first seek medical advice, about 25 per cent have metastases to the regional lymph nodes or to the submaxillary salivary gland. The presence of metastases at the time of operation has a direct relation to the prognosis; for example, Newell observed five-year survivals in 81 per cent of those without metastases.



Fig. 311. Carcinoma of lip. (Photograph by courtesy of Dr. Theo. Walsh.)

these types forms an ulcer, with induration extending from 1 to 10 mm. into the surrounding tissue. The tumors are almost exclusively epidermoid carcinomas, although there are a few basal cell carcinomas and adenocarcinomas of the upper lip. In an occasional patient a carcinoma of the lower lip is exactly opposite a carcinoma of the upper lip, and it has been supposed that one of the tumors represents an implantation metastasis (Martin, MacComb, and Blady).

Incidence. About 95 per cent of all carcinomas of the lip are on the lower lip. The greatest number are observed in patients between the ages of fifty and sixty years, and they are commoner in men in the ratio of about 19:1 (Broders).

Carcinoma of the Tongue

Carcinoma of the tongue may appear grossly in one of three forms: a papillary tu-

mor projecting above the surface of the tongue; a tumor mass within the substance of the tongue, covered by a smooth, elevated mucosa; or an ulcerative lesion with indurated edges. They are almost without exception epidermoid carcinomas, with a moderate to high degree of keratinization and formation of pearls. The most common site is the base. Metastases occur in about one-half of the cases, first to the regional nodes, and later to the thoracic viscera.

The average age is in the sixth decade. About a third of patients have a positive serologic test for syphilis and 10 per cent show leukoplakia (Gibbel, Cross, and Ariel).

Carcinoma of the Buccal Cavity

Carcinoma of the buccal cavity appears most often on the inside of the cheek, at the level of the junction of the teeth, opposite the second or third molar tooth. It is at first a small, subepithelial tumor mass, or a small ulcer, which with time enlarges and invades the surrounding tissue. All of the tumors are epidermoid carcinomas.

Metastases are present in about 50 per cent of patients on first admission to the hospital, but even in late stages metastases are rare below the clavicle. In some instances the tumor penetrates the cheek and appears on the face. With deep invasion into the tissues of the floor of the mouth, erosion and fatal hemorrhage from one of the major blood vessels of the neck is a not uncommon occurrence (Martin and Pflueger).

General Considerations of Carcinoma of the Lip and Mouth

Causal Factors. Occupation. In general, carcinoma of the lip is more common in those who are employed out of doors and are exposed to the elements. For example, it is more common in farmers than in office workers (Broders; Lawrence and Brezina).

Tobacco. There is little statistical evidence to show that tobacco itself is a causal agent in carcinoma of the lip, tongue, and cheek. Rather, it would appear to be more a matter of the way in which tobacco is smoked, and the degree of smoking (Broders). A pipe, for example, might be related to carcinoma of the lip because of: (1) the ischemia of tis-

sues produced by the weight of the pipe, (2) the chemical effects of volatile substances in the tobacco, or (3) the local heat from the pipe or the smoke. There are undoubtedly many cases on record in which carcinoma developed at the point where a pipe was held in the mouth, but there are also many other cases in which carcinoma developed on the opposite side.

Dental Hygiene. In some 40 to 70 per cent of all cases of carcinoma of the lips, tongue, and buccal cavity there is poor hygiene of the mouth and teeth. There are many instances in which carcinoma develops on the mucous membrane immediately adjacent to a broken tooth, or at a point where some ill-fitting dental appliance comes in contact with the mucosa.

Syphilis. It has long been known that about one-third of patients with carcinoma of the tongue have a positive Wassermann reaction, or present some other evidence of syphilitic infection. The specific lesion which is thought to be the forerunner of cancer of the tongue is syphilitic leukoplakia. The lesions are similar to those of nonsyphilitic leukoplakia, but the plaque is more elevated, denser, and more sharply circumscribed. There is, however, no actual reported case of established syphilitic leukoplakia becoming carcinomatous (Rous).

Leukoplakia. Leukoplakia is first observed on the mucous membrane of the tongue or the cheek as bluish white patches, which are smooth, not elevated, and frequently not sharply circumscribed, opaque and white. The epithelium is thickened, and the superficial layers are keratinized. The papillae are elongated and the subepithelial tissues infiltrated with a few lymphocytes. The adjacent blood vessels are dilated and tortuous. In from 5 to 20 per cent of patients with oral carcinoma, a history of a preceding lesion resembling leukoplakia can be secured.

Betel-Nut Cancer. Throughout the Orient, particularly in the Philippines and in India, most of the elderly people and many of the young people chew the betel nut. The chew is prepared by dipping the leaf of the buyo plant in slaked lime and wrapping it about a betel nut. Carcinoma of the mucosa of the mouth often develops at the point at which the chew is held. The practice is commoner in women than in men, and about 70 per cent of all carcinomas of the mouth in the Philip-

pinus are in women. The tumor may result from the irritating action of the lime, or from other substances contained in the leaf or in the nut (Davis; Eisen).

Multiple Tumors. It is observed that persons with oral carcinoma develop a second oral carcinoma fifteen times as frequently as would be expected from mere probability (Slaughter). This strongly suggests either that there is a constitutional factor in these tumors, or that there has been some preceding change in the mucosa of the entire buccal cavity, which leads to carcinoma. In eight of ten patients with multiple tumors leukoplakia was present.

Grading. It was with carcinoma of the lip that Broders first demonstrated the relation between the structure of a malignant tumor and the prognosis. With carcinoma of the buccal cavity, Lund divided all tumors into three classes and found five-year survivals of 36 per cent, 21 per cent, and 0 per cent, respectively. Independent studies by Martin and Pflueger resulted in percentages of 39, 20 and 0, for the same classes.

Cysts of the Lip and Buccal Cavity

Localized dilatation of the mucous glands of the lips, tongue, and cheek is not uncommon, and small, moderately firm, spherical masses, filled with a thick mucinous fluid, are formed.

Cysts with a firm, fibrous tissue wall, lined by a thick, stratified, squamous epithelium, are occasionally found in the midline at the frenulum. Some of these cysts have hair within them and sebaceous glands in the wall, and have been termed "dermoid cysts." In others the only epithelial element is the lining of squamous epithelium, and for these the term "epidermoid cyst" would seem more appropriate (Shore, Figi and Dix). It is probable that these cysts are derived from an anomaly in the fusion of the branchial arches.

Ranula. A ranula is a cystic dilatation of the duct of the sublingual or submaxillary salivary gland. The wall is thin, and composed of loose fibrous tissue and an inner lining of cuboidal or columnar epithelial cells (Shelmire). In a report from Japan, Tsuzuki found both histologic and bacteriologic evidence of syphilis in two-thirds of twenty-seven cases.

Miscellaneous Tumors of the Lip and Mouth

Mixed Tumors. About 10 per cent of tumors which show the typical histologic appearance of the mixed tumor of the salivary glands (p. 643) are found outside of the three definite salivary glands: parotid, sublingual, and submaxillary. These aberrant mixed tumors are found in the tissues of the cheek, in the palate (Eggers), in the pharynx, and in the upper lip (Eggers). They are firm, lobulated, sharply encapsulated masses (New). It seems probable that during embryologic development small masses of tissue with potentialities of forming salivary glands are misplaced, and serve as the origin of these tumors.

Rhabdomyoma of the Tongue. This is a rare tumor and may occur in infants or in adults. In most cases it is a localized, firm tumor nodule on the dorsum of the tongue, but may occasionally involve the entire tongue and produce macroglossia (Dewey). A similar tumor of the palate has been reported by Cappell.

Lymphangioma of the Tongue. These tumors may occur as nodules or as diffuse enlargement of the tongue, known as "macroglossia." In the latter condition, the epithelium is thickened and there is hyperkeratosis. The greater part of the tongue is made up of large and small anastomosing lymph channels, separated from one another by a loose connective tissue. The lymphatic spaces are lined by flattened endothelium, and not infrequently contain red blood cells. The local tumors of similar nature occur most frequently along the line of the circumvallate papillae, where the anterior and posterior anlagen fuse. It is thought that both forms of the tumor are the result of an anomalous development (Rigg and Waldapfel). Similar tumors occur in the lip and produce macrocheilia.

Lingual Thyroid

As the result of some anomaly of development all or part of the thyroid gland may fail to migrate, and masses of tissue may be found at the base of the tongue (lingual thyroid); below the tongue (sublingual thyroid); or in front of the larynx (prelaryngeal thyroid). Remnants of the duct may persist and form

cystic masses in the sublingual regions (thyroglossal duct cyst) (Goetsch). The commonest type is the lingual thyroid.

Pathologic Anatomy. Typically, the lingual thyroid occurs as a single, centrally placed tumor mass in the region of the foramen caecum. It is smooth or lobulated and usually covered by a normal mucosa. It is from pink to brown, depending upon the degree of vascularity. It is firm and elastic, and rarely exceeds 2 cm. in diameter. Occasionally, it is pedunculated. Histologically, the mass is similar to that of the normal thyroid (Ray;

rare cleft of the lower jaw, and the relatively common clefts of the lip (prealveolar), alveolar process, hard palate, or soft palate (postalveolar), or combinations of the four. The cleft may be unilateral or bilateral. The relative frequency is shown in statistics cited by Ritchie (Table 32).

The cause is unknown, but from 10 to 50 per cent are familial. The most serious consequences are interference with feeding and difficulty in articulation and speech. If repair is not undertaken early, there are secondary changes in the development of the face.

TABLE 32. FREQUENCY OF FACIAL CLEFTS

	Prealveolar Process Cleft (Others Normal)	Postalveolar Process Cleft (Others Normal)	Alveolar Process Cleft (With or Without Others)
Right.....	11	—	55
Left.....	26	—	110
Bilateral.....	1	—	51
Midline.....	—	45	—
Totals.....	38	45	216

Buchman). In a few cases the histologic picture of carcinoma has been observed in a lingual thyroid (Ashhurst and White).

Incidence. Lingual thyroid is observed in women three times as frequently as in men, and usually appears clinically at about puberty (Ray). In some 5 to 10 per cent of instances of lingual thyroid there is no thyroid gland in the normal position, a point of some importance in treatment. In about 10 per cent, cretinism has been present.

Clinicopathologic Correlation. The outstanding symptom of a lingual thyroid is difficulty in talking or swallowing, as the result of partial obstruction by the tumor mass. There is no evidence that hyperthyroidism can be attributed to a lingual thyroid. Lingual thyroid with an absent normal thyroid and cystic change in the pituitary appears to constitute a definite endocrine syndrome. Those afflicted are dwarfs, probably as a result of a deficiency of the internal secretion of the thyroid (Wells).

Congenital Anomalies of the Face and Mouth

Failure of fusion of the various parts of the face during fetal development leads to the

Cysts and Tumors Derived from the Branchiogenic Apparatus

Branchiogenic Cysts. As a result of anomalous development, a part or all of one or more of the branchial clefts may persist and form cysts or fistulous tracts. The most common fistula is that which opens on the tragus of the ear or on the skin just anterior to the tragus. The tract varies in length and is lined by squamous epithelium. It frequently becomes infected, and this secondary change is responsible for most of the symptoms. It is probable that fistulas in the midline are not related to the branchial apparatus but are a part of the thyroglossal duct. Fistulas of the internal clefts open into the pharynx about the tonsil, and are rarely observed as a clinical disease. Cysts derived from a portion of the branchial cleft cut off from the skin and from the pharynx are commonest along the upper one-half of the outer border of the sternocleidomastoid muscle. They vary in size from 1 to 5 cm., and are filled with a clear fluid. The lining is squamous epithelium, and beneath this there is fibrous tissue with numerous nodules of lymphoid tissue. In a few instances the only remnant of the branchial apparatus is a small

plaque of cartilage surrounded by fibrous tissue (Ladd and Gross; Neel and Pemberton).

Branchiogenic Carcinoma. At a later period of life a not inconsiderable number of tumors,

epithelium of a branchiogenic cyst. The presence of numerous lymphoid follicles serves as histologic evidence of this origin (Crile and Kearns).

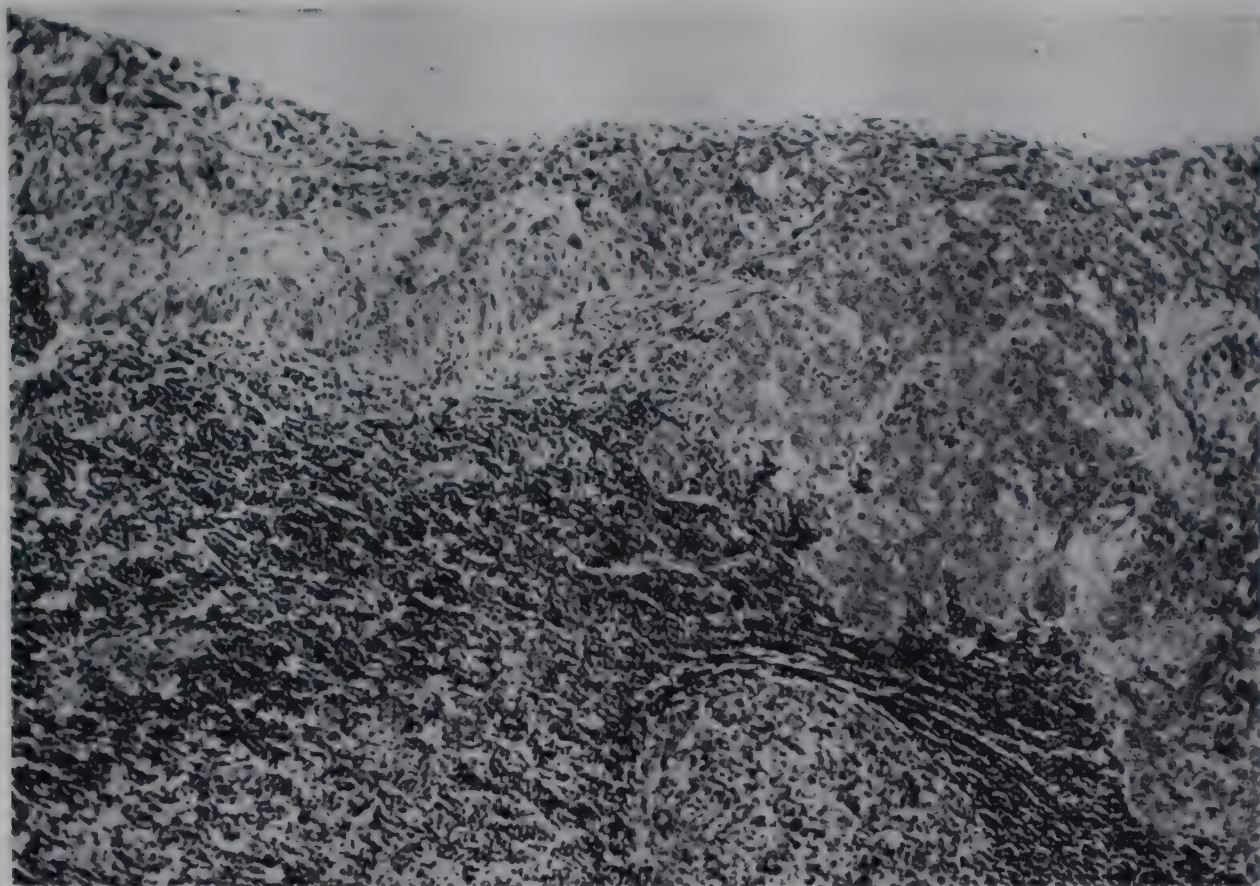


Fig. 312. Epidermoid carcinoma originating in the lining of a branchiogenic cyst.

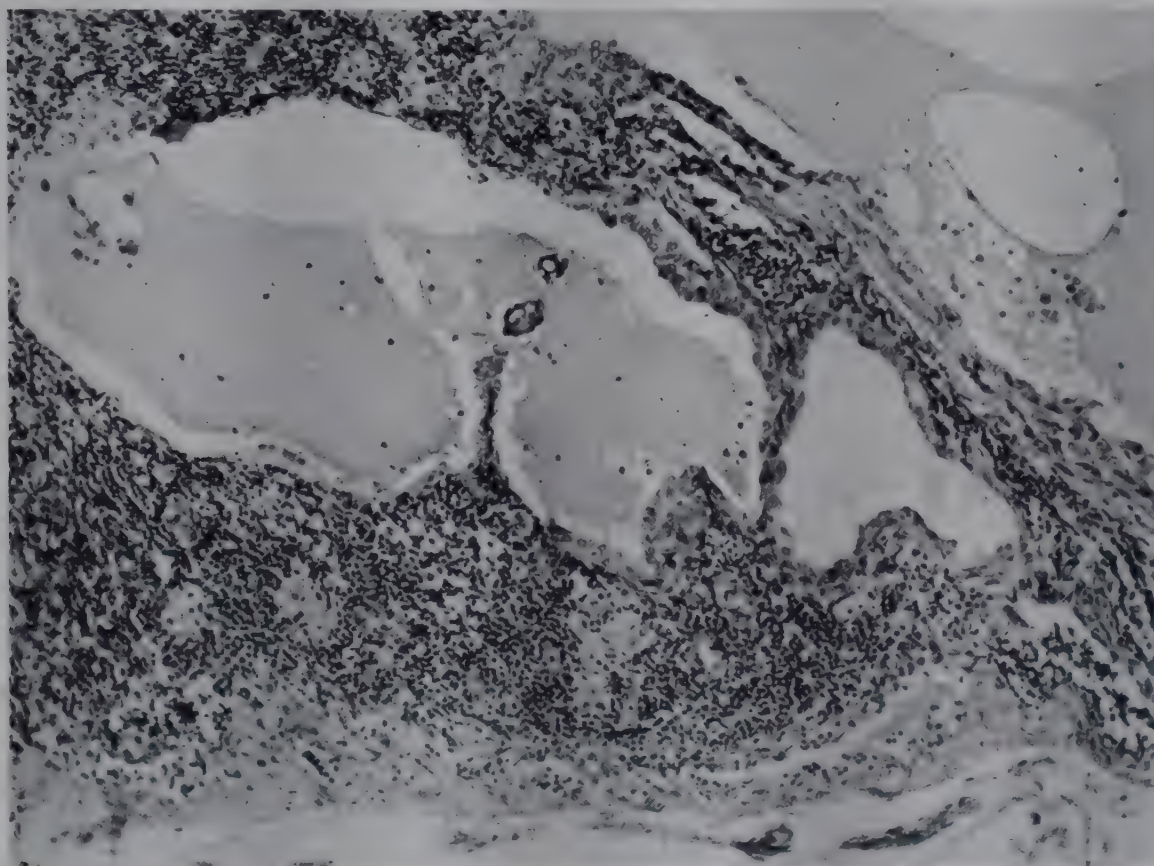


Fig. 313. "Lateral aberrant thyroid." Note epithelial structures within a lymph node. (Slide by courtesy of Dr. Nathan Womack.)

all epidermoid carcinomas, are observed in this same region. The tumor is associated in many cases with a cyst, and there seems no doubt that a carcinoma may take origin from the

Lateral Aberrant Thyroid. Single or multiple nodules located along the outer border of the sternocleidomastoid muscle on microscopic examination show a structure similar

to that of papillary adenoma and papillary carcinoma of the thyroid. It is believed by some that they represent a primary tumor of the lateral aberrant thyroid or ultimobranchial bodies (Moritz and Bayless). Others who have studied both the lateral nodules and the thyroid believe that at least some if not all tumors of the lateral aberrant thyroid are in reality metastases to the lymph nodes of a primary malignant adenoma of the thyroid. Certainly the evidence is so convincing that all patients with a lateral aberrant thyroid should

with any form of treatment, is poor (Van Metre).

Causal Factors. Little is known concerning the cause of carcinoma of the pharynx except in those cases which occur in women in association with iron deficiency anemia.

Lympho-epithelioma. Throughout all parts of the upper respiratory tract in which there is close association of epithelium with lymphoid tissue, about 10 per cent of the malignant epithelial tumors have a distinct histologic character. The epithelial cells are arranged in

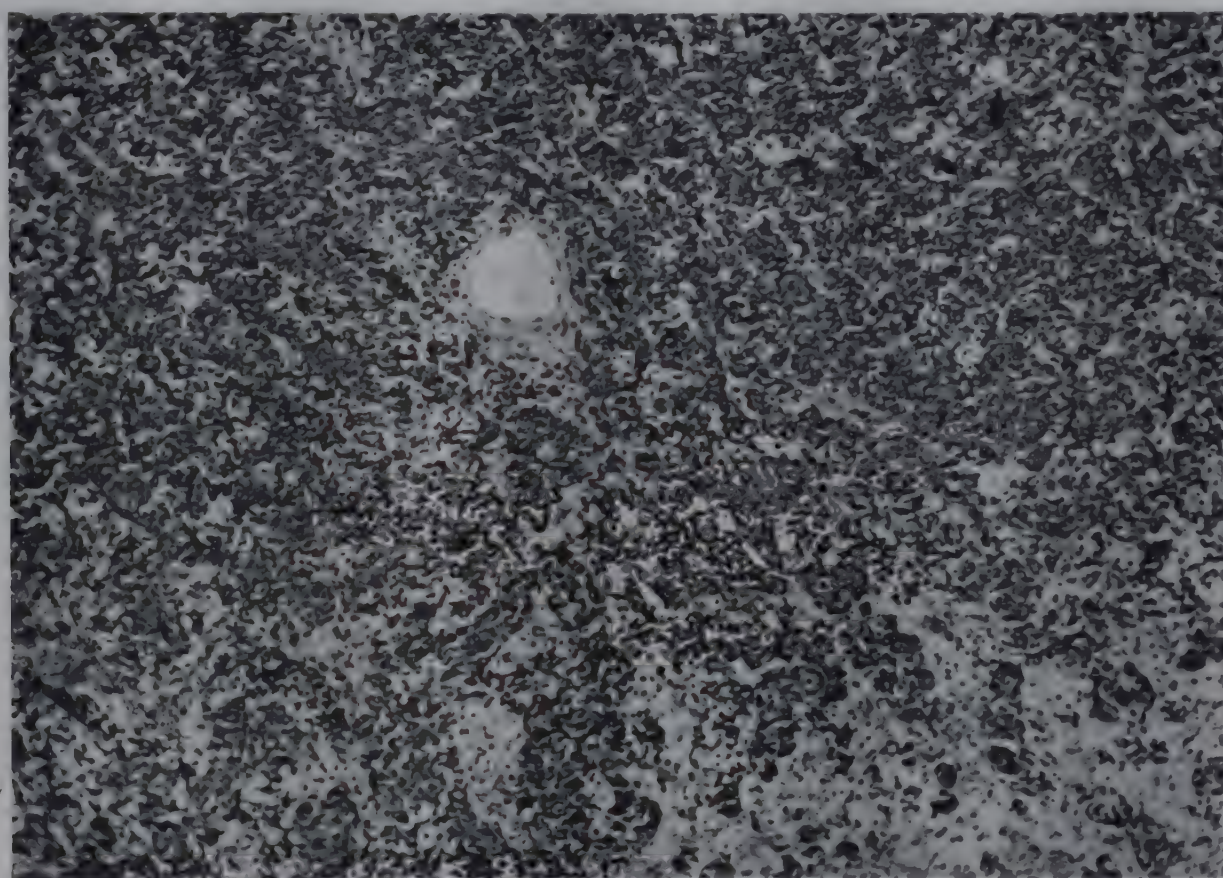


Fig. 314. Lympho-epithelioma. (Slide by courtesy of Dr. Nathan Womack.)

have a thorough examination of the thyroid (Clay and Blackman).

Tumors of the Pharynx and Nasopharynx

Carcinoma. Carcinoma of the pharynx is commonest on the lateral wall of the pharynx. It first appears as an elevation of the mucosa or as a small ulcer. Most of the tumors are highly malignant and invade the surrounding structures, extending into the nose, into the bones at the base of the skull, and occasionally into the orbit.

They are usually epidermoid carcinomas. There are early metastases to the regional lymph nodes, and later there are metastases to the thoracic and abdominal viscera, and to the bones of the vertebral column. Prognosis,

large or small sheaths and have lost most of the characteristics of epithelium. The individual cells are polygonal and show no intercellular bridges. Lymphocytes are distributed irregularly in varying amounts in the spaces between the epithelial cells. This appearance characterizes not only the primary tumor but also the metastases, and Regaud proposed the name "lympho-epithelioma" (Fig. 314).

The primary tumors are often small and soft, and rarely ulcerate. On the other hand the metastases are bulky, so that the first sign the patient complains of is an enlargement of the lymph nodes in the neck. This tumor is extremely radiosensitive, but the percentage of five-year cures has not been encouraging (Ewing).

Lymphosarcoma. Lymphosarcomas starting in the tonsil or in the smaller masses of lym-

phoid tissue within the pharyngeal mucosa may be isolated, or a part of a generalized lymphosarcomatosis. The tumor masses project into the pharynx, and on section show the characteristic white, finely granular cut surface of this type of tumor. Most are of the small cell variety. The proportion of carcinoma to lymphosarcoma of the pharynx is about 3:1 (New).

Plasmocytoma. The air passages are the most common site of the extramedullary plasmocytoma. Metastases to regional nodes are rare, but subsequent development of myeloma of bones is common (Stout and Kenney).

Fibroma of Nasopharynx. Fibromas of the nasopharynx are usually sessile, firm, nodular or lobulated, red or gray masses on the posterior wall or the vault of the nasopharynx. They may grow to fill the nasal cavities or erode the bones of the head, and appear in the accessory nasal sinuses, in the cranial cavity, or on the surface of the cheek. There is a dense irregular mass of fibroblasts with numerous small and large sinusoidal blood spaces. There is often histologic evidence of subacute or chronic inflammation.

This neoplasm occurs characteristically in young people of both sexes, usually appears at about the age of puberty, and frequently undergoes spontaneous regression at the age of twenty to twenty-five years. Recurrence after all forms of therapy is frequent (Martin, Ehrlich, and Abels).

Clinicopathologic Correlation. The signs and symptoms of these tumors depend upon two factors: (1) the great invasiveness of most of the tumors, and (2) the concentration of the anatomic structures of the neck into a small space. Involvement of the orifice of the eustachian tube results in disturbances of hearing, and may lead to infection of the middle ear. Involvement of the gasserian ganglion or the branches of the fifth cranial nerve results in neuralgia, and later in anesthesia of the face. Involvement of the sixth nerve produces ptosis of the upper lid. Invasion by tumors into the region of the jugular foramen brings on the syndrome of Jackson, from involvement of the nerves and blood vessels in this region. Invasion of the pterygoid muscle produces difficulties in chewing and may end in ankylosis of the jaw. Large tumors may obstruct the posterior nasal passages and invade

upward into the cranial cavity or into the orbit. In either instance there is disturbance of vision, and in the former there may be destruction of the pituitary gland (New).

As indicated above, most tumors of the nasopharynx are extremely malignant and give large metastases to the cervical lymph nodes early in the course of the disease.

The Plummer-Vinson Syndrome. Ahlbom found that 65 per cent of 123 women with carcinoma of the buccal cavity and pharynx gave a history of the Plummer-Vinson syndrome. This syndrome consists essentially of dysphagia, achlorhydria, hypochromic anemia, atrophy of the pharyngeal mucosa, fissures and fibrosis about the edges of the mouth, and curved fingernails. In the few autopsy studies available, the pathologic change in the pharynx is described as hyperkeratinization of the epithelium, with atrophic changes in the underlying muscle. There is slight lymphocytic infiltration into the submucosa and a moderate number of mitotic figures in the epithelial cells (Suzman). The administration of iron brings about prompt regression to normal of all the alterations noted. In the experience of Simpson, 50 per cent of all patients with this syndrome develop carcinoma of the pharynx.

Mixed Tumors of the Salivary Glands

The mixed tumor of the salivary gland type is seen most frequently in the parotid gland (89 per cent), less frequently in the submaxillary (10 per cent) and sublingual glands (1 per cent), and occasionally in other tissues of the head and neck.

Pathologic Anatomy. The typical mixed tumor is a firm, lobulated, circumscribed and encapsulated mass of gray tissue. On the cut section many combinations are seen—yellow islands of epithelium, firm fibrillar gray connective tissue, soft bluish gray translucent mucoid tissue, and islands of cartilage and bone (Sheldon).

The histologic structure is most varied and complex. Every mixed tumor consists of interstitial and epithelial elements, the proportions and relations of which vary. The epithelium may be cuboidal, columnar, spindle-shaped, or mixtures of the three. In contrast with the fibro-adenoma, there is frequently a gradual transition from epithelial to interstitial elements without a basement membrane. The interstitial component is made up of

fibroblasts, myxoblasts, chondroblasts, and rarely a few osteoblasts with the intercellular substance of each. The mucoid may be derived from epithelium.

Malignant Mixed Tumors. Some mixed tumors grow rapidly, invade the surrounding tissue, have a histologic appearance similar to that of carcinoma, and rarely metastasize to the regional nodes. Tumors of this type are commoner in younger persons, and a mass may be present for many years before the sudden onset of rapid growth.

of growth and the absence of signs and symptoms other than a mass over the parotid gland or the angle of the mandible.

In those tumors which grow rapidly, which invade through the capsule, and which recur after surgical treatment, involvement of the fifth and seventh nerves is responsible for the pain and facial palsy, respectively. Extension posteriorly may interfere with hearing.

Recurrence. As treated surgically today about 50 per cent of mixed tumors recur after periods up to forty years. Some believe that

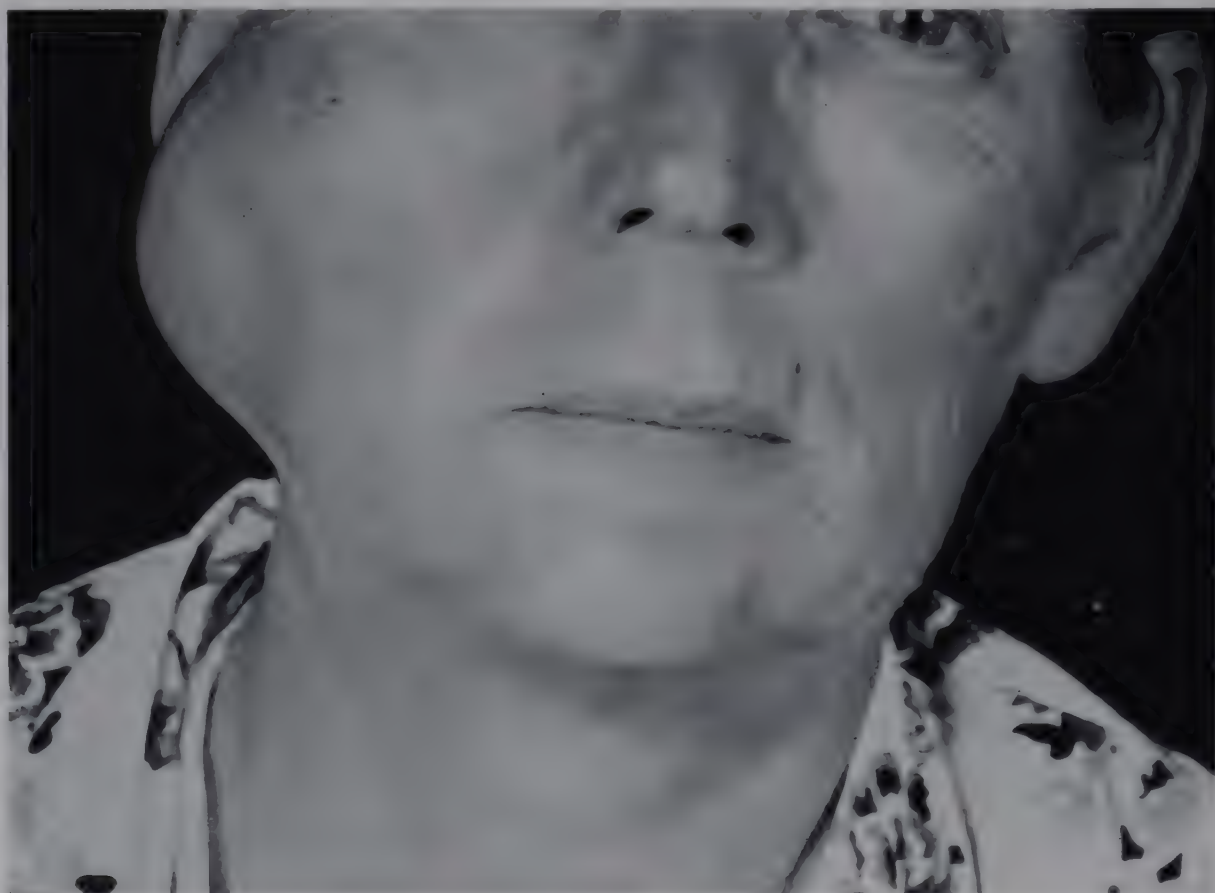


Fig. 315. Mixed tumor of parotid gland. (From the files of the Barnard Free Skin and Cancer Hospital.)

Histogenesis. The varied structure has made interpretation of histogenesis difficult. Of the many theories of origin, the most plausible is that since ectoderm in the region of the neck differentiates into mesodermal structures, tumors of mixed nature are to be expected. The lobulation, frequent difference of structure in the lobules, and occasional multiple tumors suggest a multicentric origin.

Incidence and Causal Factors. The two sides and the two sexes are affected with equal frequency. The peak age incidence is from twenty to forty-five years. The frequency is apparently greater in the white race than in Negroes. Causal factors are unknown.

Clinicopathologic Correlation. The usual long interval between the appearance of the tumor and the seeking of medical advice—six to ten years—is indicative of the slowness

histologic appearance is correlated with recurrence (Stein and Geschickter), while others conclude that it is not (McFarland).

Variants and Other Tumors of the Salivary Glands. In addition to the mixed tumor, rare neoplasms described as adenoma (McFarland), cylindroma, oncocytoma (Meza-Chanez), and lymphadenoma (Robinson and Harless) have been reported. It is highly probable that these are variants of the mixed tumor, but more study is required. A distinctive variety of tumor of the salivary glands is that containing both mucin-forming cells and squamous epithelium. They may be benign or malignant (Stewart, Foote, and Becker).

Salivary Calculi

The submaxillary gland and duct are the most frequent sites of salivary calculi. The

explanations offered for this are: greater susceptibility to external trauma and bacterial infection, higher content of mucin in secretion, and the frequency of anatomic peculiarities of the duct. Calculi are usually asymptomatic, unless there is obstruction with or without secondary infection (Tholen). The calculi are single or multiple and composed chiefly of calcium phosphate and carbonate (Greenfield).

Congenital Atresia of the Esophagus

The usual congenital anomaly of the esophagus is remarkably constant in pattern. The pharynx divides into larynx and esophagus in the usual fashion. From 1 to 5 cm. below this point the esophagus ends blindly. There is hypertrophy of the muscle of the sac, present at birth. From below, the esophagus runs upward 4 to 7 cm. from the cardia, and joins the trachea or bronchi just above or below the bifurcation, through a crescent-shaped orifice. The two segments of the esophagus are usually separated by about 1 cm., and are connected by a fibrous cord. The spilling of ingested food and gastric juice into the lung sets up a necrotizing bronchopneumonia (Rosenthal).

Acute Esophagitis

A variety of changes in the esophagus were for many years considered to be postmortem autolysis, but recent investigation indicates that they take place before death.

Pathologic Anatomy. The essential changes are ulceration and inflammation, most conspicuous in the lower third. The minimal lesion is a denudation of a normally white opaque epithelium in a fashion to form multiple, isolated or confluent, linear ulcers. The ulcers may be partly covered by a fibrinous exudate. With the increase of necrotic superficial tissue there is hemorrhage and conversion of the blood by the gastric juice in the lumen to a black eschar. As the deeper layers of the wall are exposed to bacteria and to gastric juice, there is a severe phlegmonous inflammation. The wall is thickened, firm, and edematous. There are necrosis and infiltration with leukocytes. The terminal event is perforation, usually into the left pleural cavity. In a large or small region the wall is defective,

and the edges are soft and friable, a condition known as "esophagomalacia."

Pathogenesis. Most patients are debilitated and seriously ill from some other disease. It is probable that slowing of the circulation, thrombosis, and other factors render the esophageal mucosa more susceptible to digestion by gastric juice and to trauma.

Clinicopathologic Correlation. There is vomiting, but it is not clear whether it is a cause or effect. In some patients the vomitus contains blood, apparently derived from the ulcers of the esophagus (Bartels).

Causes and Effects of Obstruction of the Esophagus

Causes. Aside from carcinoma, to be discussed later (p. 647), there are a number of lesions which cause obstruction of the esophagus.

Cicatricial Stricture. Following ingestion of strong corrosive poisons, the ulceration and inflammation heal by fibrous replacement. With contraction of the scar in six to ten weeks, there is a diffuse or focal stenosis of the lumen (Clerf). Similar lesions are seen after scarlet fever (Vinson).

Cardiospasm. This interesting condition, producing obstruction of the esophagus, occurs more commonly in men, during the third and fourth decades. In radiographs there is a smooth funnel-shaped constriction at the cardia and dilatation of the lumen above. Anatomically, there is little to be seen except the dilatation and hypertrophy. The size of the esophagus is so great as to encroach on the other thoracic organs and produce respiratory distress and pain (Bull). The rare idiopathic hypertrophy of the esophageal muscle may represent a compensated achalasia (Wood).

Foreign Bodies. Foreign bodies are seen in the esophagus half as frequently as in the respiratory tract. The usual objects are bones, large pieces of meat, dental plates, safety and straight pins, and metallic trinkets.

Pressure from Without. With many tumors of the mediastinum, with large aneurysms, and with excessive dilatation of the heart, the esophagus may be compressed from without or invaded by neoplastic tissue (Mosher).

General Effects. The effects of obstruction of the esophagus are many, and to some degree vary with the cause.

The effect common to all is dilatation proximal to the point of obstruction. One of the most serious consequences is aspiration of ingested food and fluid into the respiratory passages. The foreign material plus bacteria soon induces bronchopneumonia and multiple abscesses. The patient who has advanced esophageal obstruction is characteristically dehydrated and emaciated (because of inability to eat and drink), and has a severe respiratory infection.

Aberrant Mucosa in the Esophagus. Heterotopic mucosa may be present in 70 per cent of all esophaguses. The usual types are gastric mucosa with and without parietal cells, and superficial ciliated cells (Rector and Connerly), more common in the upper third.

Diverticula of the Esophagus

Pulsion Diverticula. Pulsion diverticula occur almost exclusively at the upper end of



Fig. 316. Diverticulum of esophagus. (Radiograph by courtesy of Dr. Sherwood Moore.)

With sharp foreign bodies and in carcinoma either within or without the esophagus, trauma or necrosis may lead to perforation. If the mediastinum is entered, severe cellulitis may follow and cause death within a few days (Grace and Irwin). With perforation in the upper third an interstitial emphysema of the tissues of the neck may follow. Occasionally, the perforation enters the trachea or bronchi, and a tracheo-esophageal fistula is established. An aneurysm pressing from without may penetrate the wall and rupture into the lumen.

the esophagus, and are in reality diverticula of the posterior wall of the hypopharynx. The orifice of the sac is in the midline between the fibers of the cricopharyngeus muscle. The sac dissects caudally between the post-tracheal and the prevertebral fascias, and may contain as much as 300 cc. of fluid. The sac is lined with squamous epithelium which shows a variable degree of keratosis.

Pulsion diverticula occur most frequently in older people. They apparently result from pressure from food within the pharynx just

above the inferior constrictor muscle (Perone).

Traction Diverticula. Traction diverticula of the esophagus are commonest at the level of the bifurcation of the trachea. They are usually small, and rarely hold over 5 cc. of fluid. They not infrequently extend in a cephalad direction. At the tip of the diverticulum the tissue is attached to a pigmented lymph node, which, in about 75 per cent of cases, is the seat of an old tuberculous process (Wallace).

Clinicopathologic Correlation. The symptoms of diverticulum of the esophagus depend upon two factors: (1) the retention of fluid and food within the sac, and (2) obstruction of the esophagus by the expanding diverticulum. The symptoms caused by fluid and food

all there is fixation to surrounding structures, and at times direct extension to the pericardium, pleura, and mediastinum. The ulceration may extend into an adjacent blood vessel, into the tracheobronchial system, or into the pleura or pericardium. In the first, serious or fatal hemorrhage is the result, and in the second and third, severe infection, usually necrotizing or purulent. The esophagus above the point of obstruction is dilated and the muscle hypertrophic.

The common sites are the pharyngo-esophageal junction, the middle third, and the lower few centimeters. In all there are metastases to the lymph nodes of the posterior mediastinum. With tumors of the upper third, the cervical nodes are involved, and with tumors of the lower third the nodes in the gastro-

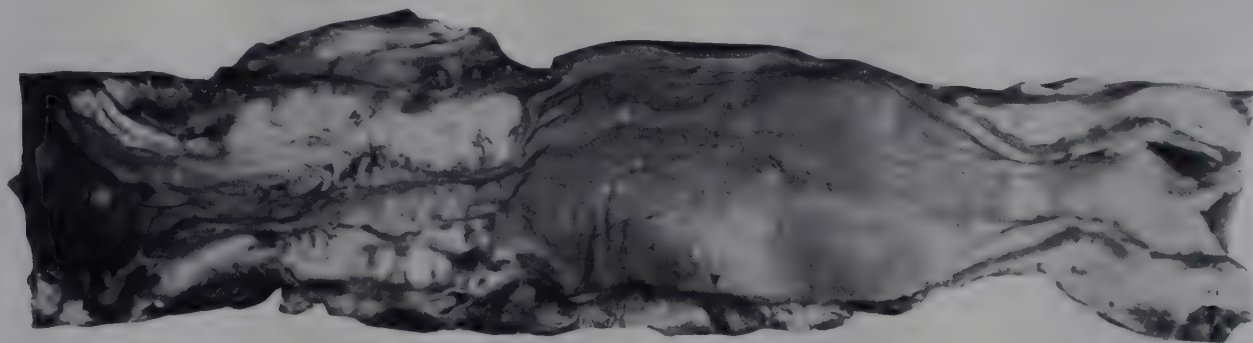


Fig. 317. Carcinoma of esophagus.

in the sac are a gurgling sound in the neck, and paroxysms of coughing, from an overflow of fluid into the respiratory tract. If the sac is large, there may be retention of food, regurgitation and decomposition, and foul breath (Lahey).

Carcinoma of the Esophagus

Carcinoma of the esophagus constitutes about 5 to 7 per cent of all carcinomas in men, and is the commonest cause of dysphagia in older persons.

Pathologic Anatomy. There are three types of carcinoma of the esophagus: (1) ulcerative, (2) polypoid, and (3) diffuse infiltrative. The *ulcerative* is the usual form. It starts as a small mucosal lesion, and spreads to involve the entire circumference of the esophagus. There is a large, deep ulcer with a firm base and elevated, indurated margins. The *polypoid* type is a fungative mass projecting into the lumen, and the *diffuse infiltrative* type converts the greater part of the esophagus into a firm, constricted tube, without ulceration. In

hepatic omentum are affected. Late metastases are seen, chiefly in the lungs and liver.

About 90 per cent of carcinomas of the esophagus are poorly differentiated epidermoid carcinoma, and 10 per cent adenocarcinoma.

Incidence. The ratio of men to women is at least 5:1, and almost all patients are over forty years of age. The maximal incidence is in the sixth decade. Tumors of the upper third are more common in women (Vinson).

Causal Factors. Clinical statistics suggest that persons who bolt their food, consume excessively hot food and drink, eat at irregular intervals, use alcohol in excess, and have poor dental hygiene are more prone to develop esophageal carcinoma. Anatomic studies indicate that minor anomalies of the epithelium and heterotopic types of epithelium are contributing factors.

Clinicopathologic Correlation. Carcinoma of the esophagus brings about clinical signs and symptoms because of (1) obstruction, (2) infection, and (3) late metastases.

The obstruction comes on gradually, with increase in size and invasion and contraction

of the wall. Since the consumption of food is limited, there is a progressive loss of weight and dehydration. Iron deficiency anemia from bleeding into the ulcer and from inadequate intake may not be evident because of hemocentration.

Infection may be manifested by invasion of surrounding tissues through the ulcerated tumor and by the overflow of food and secretions in the lung. Later a tracheo-esophageal fistula may contribute. The characteristic changes are bronchopneumonia and multiple abscesses of the lungs. The effects of late metastases vary with the location. The average survival time after the diagnosis is made is less than a year.

Miscellaneous Tumors of the Esophagus. Neoplasms other than carcinoma are rare, and only occasionally cause symptoms. The more notable are leiomyoma, angioma (Vinson; Moore; and Bowing), adenoma (Moersch and Broders), and lipoma (Vinson).

Diaphragmatic Hernia

Pathologic Anatomy. Hernias of the abdominal viscera may occur as the result of an incomplete formation of a part of the diaphragm; of incomplete development of the muscle of the diaphragm, thus leaving a weak place; of nonfusion of the pleural peritoneal membrane; or of inaccurate apposition of the diaphragm to the structures which normally perforate it, particularly the esophagus (Weinberg; Polley; Bremer).

The most common diaphragmatic hernia is a small protrusion of the stomach along the left side of the esophagus, known as an "esophageal hiatal hernia." Two varieties are recognized: one in which the esophagus is of the normal length and the hernia is formed as the result of a weakness of the diaphragmatic muscle about the esophagus; the other variety is associated with a congenitally short esophagus, in which a portion of the stomach projects into the thorax as a thoracic stomach (Brick).

The most spectacular diaphragmatic hernia is the congenital type resulting from absence of a hemidiaphragm, usually the left. Children with this type of hernia rarely live more than a few days, and the greater part of the abdominal viscera are found in the left pleural cavity. There is in consequence a displacement

of the heart to the right and a complete compression atelectasis of the left lung. A similar condition is found in adults following severe trauma to the thorax or abdomen, with rupture of the diaphragm, again usually on the left side.

Causal Factors. In general, diaphragmatic hernias, aside from the congenital type, are caused by increased intra-abdominal pressure, which pushes the viscera into the lining of the abdominal cavity. If in this lining there is a weak point, the increasing pressure results in an evagination of the peritoneum and the formation of a hernia.

Clinicopathologic Correlation. The symptoms of a diaphragmatic hernia depend upon the size and content of the sac. With increasing size of the sac there is a decreasing space within the thorax, with symptoms of respiratory embarrassment—dyspnea and cyanosis. If the liver is the herniated organ, there may be few symptoms, but if the stomach and intestine are within the thorax, digestive disturbances and even intestinal obstruction are not uncommon, since the mesenteries of these structures are elongated and the hollow tubes are kinked, either within the sac or at the mouth of the sac.

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LXXXI

Diseases of the Stomach and Duodenum

Although the stomach and duodenum have different physiologic functions, from the standpoint of the pathologist and surgeon they have much in common. Hence, diseases of these organs are discussed together in this chapter.

Diverticula of the Stomach

The stomach is one of the unusual points in the gastro-intestinal tract for the formation of diverticula. When found, they may be congenital or acquired. They are usually 2 to 3 cm. in length and 1 to 2 cm. in diameter. About one-half of all instances occur in the fundus and the other half in the region of the pylorus. In most patients there are no symptoms or signs which can be clearly identified with the presence of the diverticulum (Rivers, Stevens, and Kirklin).

Foreign Bodies in the Stomach

Foreign bodies in the stomach may be grouped into three classes, those which are directly swallowed, those which are formed within the stomach from smaller masses of ingested material, and those which come to lie in the stomach as the result of external trauma, a surgical operation, or a fistula from surrounding organs. The swallowed objects include needles, pins, screws, and various small blunt objects which are likely to be available to children. The foreign bodies formed within the stomach are known as "bezoars," and may be qualified on the basis of the type of material which enters into their composition. The most common foreign body introduced from without is a gallstone, which enters the stomach through a cholecystogastric fistula (Segal and Morton).

Chronic Atrophic Gastritis

Pathologic Anatomy. The mucosa of the stomach in atrophic gastritis is grayish pink,

gray, or greenish gray. Through the mucosa, which is thin and firm, the blood vessels of the submucosa are clearly visible as red arborizations. In general, the atrophic changes are more marked in the fundal part of the stomach, but they may involve the entire stomach or occur irregularly. The mucosa is thin, and contains only a few glands. The interstitial tissue is fibrotic, and is infiltrated with lymphocytes and plasma cells. The epithelium of the glands and crypts is similar to that on the surface, and there is no longer a distinction between chief and parietal cells. Within the epithelium there are a moderate number of vacuoles filled with mucus. In localized areas there may be hyperplasia of the mucosa even to the formation of a pseudopolyp (Hebbel).

Types. Chronic atrophic gastritis may be a primary disease, may be secondary to pernicious anemia, sprue, or carcinoma of the stomach, or may follow the ingestion of a corrosive substance. In some instances it follows an acute gastritis (Magnus).

Causal Factors and Pathogenesis. The cause of primary chronic atrophic gastritis is unknown. The incidence of the disease increases with age, and it is possible that it represents senile involution. The fact that the administration of liver extract or of ventriculin results in cure in some cases would indicate that it is a deficiency disease.

Clinicopathologic Correlation. In most cases of chronic atrophic gastritis there is a relative or absolute anacidity, but there is rarely an absolute absence of pepsin. The symptoms are indefinite, and no exact correlation between pathologic and physiologic changes and signs and symptoms is possible. The patients complain of fulness, belching, slight pain, and loss of appetite.

Hypertrophic Gastritis. In a variety of conditions the gastric mucosa appears to be thick-

ened, and is arranged in a mosaic pattern, as viewed from the luminal surface. The current view is that it represents an effect of irregular contraction of the muscularis mucosa.

Peptic Ulcer

The peptic ulcer is so named because of the assumed causal role of the peptic juices of the stomach.

Pathologic Anatomy. The typical chronic peptic ulcer is a single ulcer, less than 25 mm. in diameter, along or near the lesser curvature in the pyloric half of the stomach,

There are four distinct zones in the floor of the peptic ulcer. Toward the lumen is a layer of purulent or fibrinopurulent exudate, more prominent in active ulcers and under the overhanging edges. It is easily detached from the second zone of fibrinoid necrosis, consisting of a narrow, dense, acidophilic layer with scattered nuclear debris. Next is the zone of granulation tissue, which gradually shades into the most peripheral zone of fibrosis. The granulation tissue is infiltrated with many eosinophils, lymphocytes, polymorphonuclear leukocytes, and a few mast cells.

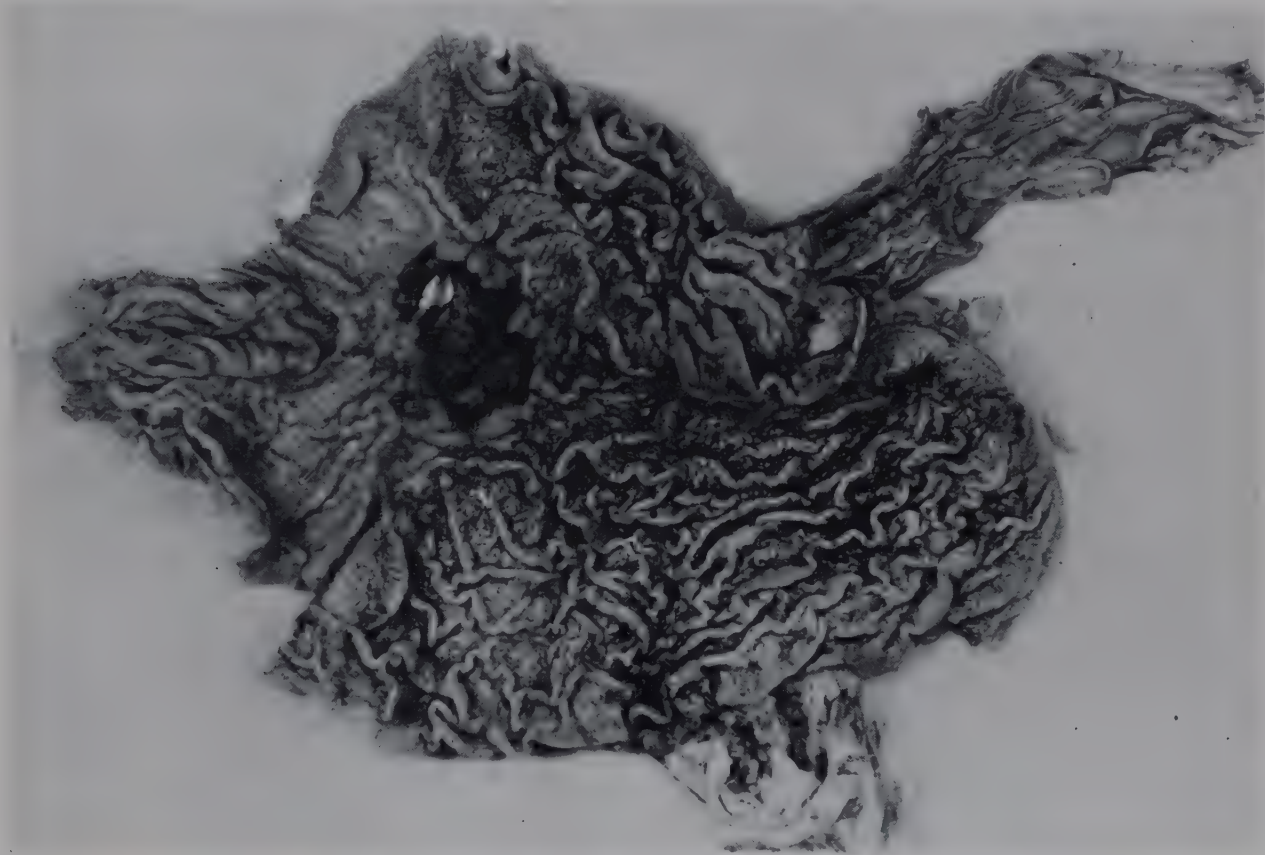


Fig. 318. Peptic ulcer of stomach with perforation.

or on the anterior or posterior wall of the first 3 cm. of the duodenum.

The outline is round or oval, and regular. The shape of the excavation varies from funnel-like in the subacute and active lesions to globular or cylindrical with overhanging edges in the chronic forms. During activity the margins are red, edematous, elevated, firm, and overhanging, while healing is characterized by a flattened, pale, indurated edge.

Acute ulcers involve only the mucosa and submucosa. Penetration through the muscularis is an almost constant feature of chronic ulcers. In the adjacent serosa there are fibrosis, and frequently adhesions to surrounding structures. If a solid viscus such as the pancreas or liver is reached, there is fibrosis or ulceration into it.

About the nerves there are fibrosis and cellular infiltration. The arteries, and to a less extent the veins, show proliferation of the intima and thrombi in the lumen. If there has been severe hemorrhage, an artery in the base of the ulcer with erosion of a segment of the vessel or a small aneurysm will be observed. The muscularis mucosa and the muscularis in chronic ulcers are completely interrupted and may be deformed by the cicatricial contraction. The mucosa in active ulcers ends abruptly, and the marginal tissue is edematous and infiltrated with cells.

Healing and Healed Chronic Ulcers. Magnus estimates that 10 per cent of all individuals some time in their life have peptic ulceration usually as a part of acute gastritis. Careful examination of the stomach at autopsy

in unselected cases reveals about as many healed as active peptic ulcers. The process of healing involves growth of the epithelium over the surface, fusion of the muscularis mucosa and muscularis, contraction of fibrous tissue and approximation of the ends of the severed muscularis, and filling of the defect with dense fibro-elastic tissue. The regenerated epithelial layer is thin, contains no oxyphilic cells, and frequently contains glands of the duodenal or interstitial type (Taylor). With most healed ulcers there is a radiating avascular scar. In

peritoneal cavity or into surrounding tissue or an adjacent viscus. Gastric ulcers along the lesser curvature perforate into the gastro-hepatic omentum or into the liver. Some of these ulcers, and ulcers on the superior wall of the duodenum, perforate in such a way that a fistulous tract is formed along the surface of the liver into the subphrenic space, where a large abscess is formed. Ulcers on the posterior and medial walls of the duodenum perforate into the pancreas and produce a large or a small focus of pancreatic necrosis.

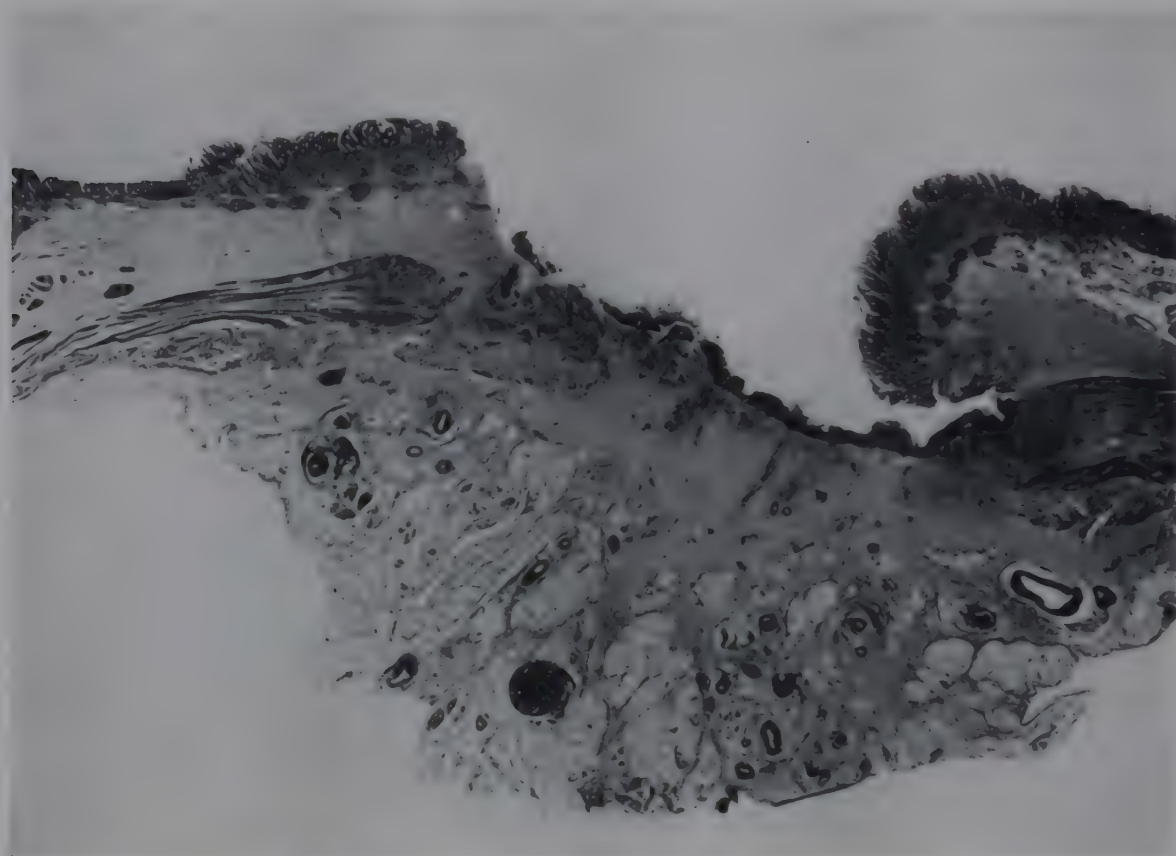


Fig. 319. Peptic ulcer. Note the sloping edge on the proximal side, the mucosal hyperplasia on the edges, interruption of the muscularis, and thickening of the serosa.

the first part of the duodenum small diverticula represent healed ulcers.

Complications. *Hemorrhage.* In about 10 per cent of all cases of chronic peptic ulcer there is at some time during the course of the disease extensive hemorrhage from the bed of the ulcer, which in many instances leads to death by exsanguination. If death does not occur, from 500 to 1000 cc. of blood may be poured into the gastro-intestinal tract. There follows an increase of the blood urea nitrogen from the digestion and absorption of this large amount of blood. Shock, dehydration, starvation, or impaired renal function may increase the degree of this phenomenon (Yuile and Hawkins).

Perforation. From 15 to 20 per cent of peptic ulcers perforate through the wall of the stomach or duodenum, either into the free

This type of pathologic change is typically associated with extreme pain, greater than in any other type of chronic peptic ulcer. Perforation into the peritoneal cavity is followed by an acute fibrinous peritonitis. If the patient is operated upon within six hours after perforation, the mortality rate is about 15 per cent, but after thirty hours it is 80 per cent (Sangster).

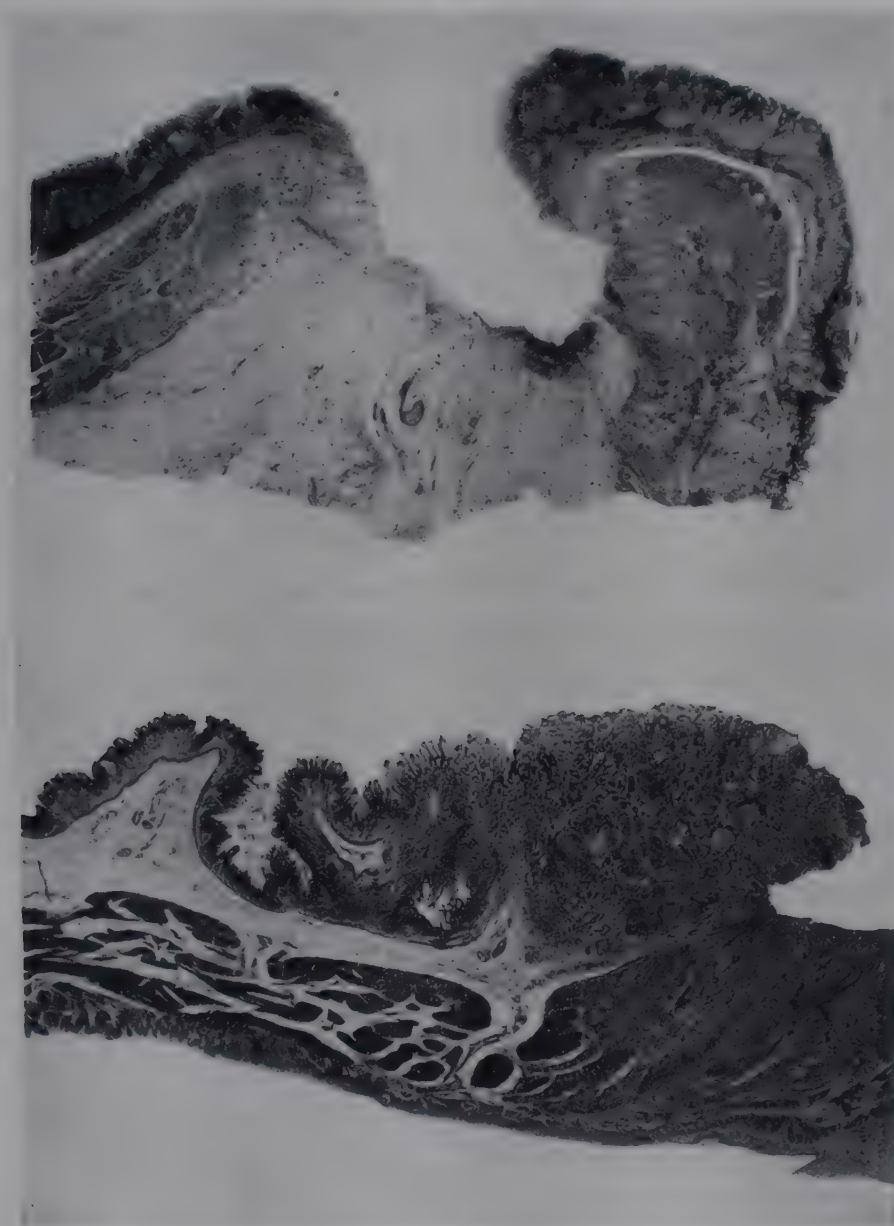
The Relation of Gastric Ulcer to Gastric Carcinoma. There can be little doubt that a certain percentage of carcinomas of the stomach develop from chronic gastric ulcers. Figures vary from 70 per cent (MacCarty and Broders) to as low as 2 per cent, for the percentage of gastric ulcers which also show carcinoma either in the edge or in the base. These differences result in large part from the disparity in the criteria which are employed

for the diagnosis of carcinoma. A more logical approach is the use of obvious anatomic criteria such as those proposed by Stewart. On the basis of a large experience, Stewart found that the typical chronic gastric ulcer causes destruction of the muscularis, and that the tissue about the ulcer shows obliterative endarteritis and organized thrombophlebitis, and

tous change. It must remain for future investigation to explain this difference.

Incidence. Peptic ulcer of the esophagus is rare (Dick and Hurst). Clinically manifest duodenal ulcer is commoner than gastric ulcer, in the ratio of 2 or 3:1; while if incidental ulcers found at autopsy are considered, gastric ulcer is more common in the ratio of about

A



B

Fig. 320. *A*, Carcinoma in the edge of a peptic ulcer. *B*, Ulceration in a carcinoma. See text for differentiation.

that, on the other hand, primary carcinoma of the stomach invades but does not destroy the muscularis and does not exhibit vascular changes in the adjacent tissue. He reasoned that a carcinoma with ulceration in which the muscularis was destroyed represents a cancer starting in a preexisting ulcer. With these criteria he found that about 9.5 per cent of all chronic gastric ulcers become cancers and about 17 per cent of all cases of cancer show evidence of originating in a chronic ulcer.

In contrast to the gastric ulcer, the chronic duodenal ulcer almost never shows carcinoma-

3:2. Gastric ulcers so found are usually small and show less fibrous tissue than the duodenal ulcers. These observations can mean only one thing: that the duodenal ulcer shows a greater tendency to be a large, progressive chronic ulcer, while the gastric ulcer is more likely to be acute or subacute, with a tendency toward healing. Both the clinical and the silent ulcers are commoner in men in the ratio of about 9:1. Peptic ulcer shows about the same incidence in the Caucasian race throughout the world (Portis and Jaffe). The age incidence is very low in children (Donovan and

Santulli), reaches a peak in late adulthood, and decreases only slightly in old age (Kiefer and McKell).

Causal Factors. Constitution. Other members of the family of a patient with peptic ulcer show a high incidence of gastric disturbances in general, and of ulcer in particular (Drossner and Miller). Of additional interest is the observation that there are a greater number of men in ulcer families and a greater number of women in families with gallbladder disease, corresponding to the incidence of the two diseases in the two sexes (Draper and Touraine). In general, the patient with peptic ulcer is thin, normal in weight or underweight, excitable, and physically active.

Age and Sex. In adults, peptic ulcer is distinctly a disease of men; while in children below the age of six years, ulcer is more common in girls than in boys. From the age of seven to the age of twelve there is a slight preponderance in boys. This would suggest that there is some physiologic or anatomic change in boys at puberty which is a causal agent in the formation of ulcers (Saltzstein, Farbman, and Sandweiss).

Gastric Juice. The direct relation between active gastric juice and peptic ulcer is borne out by the low incidence of ulcers in patients with atrophic gastritis and achlorhydria (as in pernicious anemia), and the occurrence of peptic ulcer in parts of the gastro-intestinal tract where there may be heterotopic gastric mucosa: in the esophagus at the level of the cricoid cartilage and in the distal few centimeters (Taylor); in the stomach and duodenum; in the jejunum after gastrojejunostomy; and in Meckel's diverticulum. It is worthy of note that ulcers in the esophagus and intestine are almost always adjacent to, rather than in, the heterotopic gastric mucosa. Further evidence is given by the observation that a patch of intestinal mucosa in the stomach will induce a lowering of the acid content of the gastric juice and apparent healing of gastric ulcers (Andrus, Lord, and Stefko). It would be of interest to determine whether or not heterotopic intestinal mucosa is present in stomachs with ulcers (Magnus).

The cause of the rare primary jejunal and ileal ulcer not associated with heterotopic mucosa is unknown (Beery and Dailey).

Nutrition. In Russia during the period of

extreme starvation from 1918 to 1922, the incidence of chronic peptic ulcer in routine autopsies increased to 12 per cent. In the immediately preceding and following periods the incidence had been from 3 to 4 per cent. During this same time the incidence did not increase in the region about the Black Sea, where the starvation was not so severe. There are a number of possible explanations of this phenomenon: coarse food, which may injure the gastric mucosa; ptosis of the abdominal viscera from starvation; hyperacidity, which is known to be associated with starvation; and the psychic state of the person in an area where there is inadequate food for himself and for his family (Hamperl). The higher incidence of peptic ulcer in Holland than in England is attributed to the ingestion of highly spiced foods by the Dutch. A low protein diet over a period of time results in the formation of chronic duodenal and gastric ulcers (Weech and Paige). It is unlikely that hot and cold foods are of any importance as causal factors.

Nervous Influences. One of the earliest ideas concerning the origin of ulcer was that it represented in the beginning a small area of ischemic necrosis, brought about either by emboli or by vascular spasm. It is possible that nervousness and anxiety may induce contraction of the smaller blood vessels. It is significant that the typical patient with ulcer is tall, thin, nervous, and active. The reported favorable influence of vagotomy is indicative of a nervous influence.

Infection. In about 60 per cent of instances of acute peptic ulcer, acute infection (peritonitis, septicemia, pyemia) appears to act in a causative role. On the other hand, the relation of chronic infection to chronic ulcers is not clear. Some report a high incidence of dental and nasopharyngeal infection and chronic appendicitis in patients with ulcer.

Trauma. There is no objective evidence that a single external trauma to the abdomen either causes or aggravates a chronic peptic ulcer (Gray).

Peptic Ulcer in Association with Burns. In some 2 to 4 per cent of persons with extensive third-degree burns of the skin, acute ulcers of the stomach and duodenum appear, known as "Curling's ulcers." These ulcers are sharply outlined and usually do not extend beneath the submucosa, but perforation has been reported. Of 92 such cases collected

from the literature, 71 were duodenal ulcers and 16 were gastric ulcers, and in 5 cases there was both a duodenal and a gastric ulcer. Many theories have been proposed to explain this association of acute peptic ulcer and superficial burns, but none has been proved (Harkins).

Acute Ulcers. Hemorrhagic Erosions. In a great variety of conditions such as chronic passive congestion and repeated vomiting, small acute ulcers develop throughout the stomach, somewhat larger and more numerous in the pyloric part. There is simple autolysis of the mucosa of the stomach with a surrounding zone of edema, congestion, hemorrhage, and infiltration with lymphocytes and polymorphonuclear leukocytes. It is generally supposed that these acute ulcers are formed during the agonal state, because of the inadequate circulation during this period. The ulcers which occur with repeated vomiting are attributed to trauma from the active reverse peristalsis. Acute and subacute ulcers may form in the stomach in association with acute gastritis or with atrophic gastritis (Rodgers and Jones).

Gastromalacia. A certain number of persons suffering from some disease of the base of the brain have multiple erosions in the mucosa of the stomach and duodenum, or digestion of the fundus of the stomach and at times the adjacent esophagus. The digestion may lead to perforation and the presence of gastric contents in the peritoneal or in the left pleural cavity. In the less advanced stages of the change, only the mucosa of the fundus is autolyzed, so that the lining of the stomach appears as a ragged, light greenish gray membrane, on a firm white muscularis.

Until recently it was generally assumed that the autolysis of the fundus of the stomach, termed "gastromalacia," was a postmortem change; but careful histologic examinations and correlative studies show that it undoubtedly develops during the agonal state. Similar lesions have been produced in animals by injury to certain parts of the base of the brain, and by the injection into the ventricles of drugs which produce vasospasm, or which stimulate the parasympathetic centers. Experimental observations strongly suggest the presence in the diencephalon of a parasympathetic center, probably in the tuber cinereum. From this center there are tracts which pass caudally

to the medulla, and there connect with the vagal nuclei. A lesion of the tuber cinereum, or of the brain-stem involving the connections, may result in lesions of the stomach (Wyatt and Khoo).

Secondary Effects of Treatment. Alkalis. The accepted medical treatment for chronic peptic ulcer is the administration of a bland diet and of alkaline powders, both directed toward resting the stomach and neutralizing the hyperacidity which is usually present. If the administration of alkalis is continued over months, there results a mild alkalosis (Eisele), particularly if there is preexistent renal disease. Hypochloridemia may also develop. During therapy with alkalis the urinary excretion of solids is doubled, and a number of these patients develop urinary calculi (Eisele).

Jejunal Ulcer. One of the most popular surgical treatments of chronic peptic ulcer is a short-circuiting of the gastro-intestinal tract by the establishment of an opening between the stomach and the jejunum—gastro-jejunostomy. About 4 per cent of patients so treated return in a period of from a month to a year with a newly developed chronic ulcer in the region of the anastomosis (Archer). The jejunal ulcer is identical with the chronic peptic ulcer except that it is usually of shorter duration and therefore shows less fibrosis. There are the same complications, hemorrhage and perforation (Wright). Perforation may occur into the free peritoneal cavity or into the transverse colon, with the establishment of a gastro-jejunocolic fistula (Stein). In this latter condition it is at once evident that the greater part of the gastro-intestinal tract is short-circuited, and that food taken into the stomach is immediately diverted into the colon, and not absorbed. These patients therefore show starvation, general vitamin deficiencies, and low plasma protein (Ransom).

Clinicopathologic Correlation. The clinical symptoms and signs of chronic peptic ulcer are directly dependent upon the anatomic and physiologic change produced by the ulcer (Ivy). Dyspepsia is probably related to the altered character of the gastric juice, possibly to the hyperchlorhydria. Vomiting is in some instances a physiologic phenomenon, and in others results from actual anatomic obstruction by the scar tissue of an ulcer in the region of the pylorus. Blood in the vomitus or blood

in the stool—melena—is evidence of hemorrhage from the vessels in the base of the ulcer. During the passage through the small intestine, the character of the blood is altered so that the typical tarry stool is produced. But it should be recognized that the tarry stool is evidence of moderate to severe hemorrhage—at least 80 cc. In many instances the crater of the ulcer, extending outward from the wall of the stomach, can be identified in x-ray films. X-ray examination is of further value in determination of the degree of pyloric stenosis, since the retention of barium within the stomach for a period longer than six hours is pathologic.

ach. It is probable that many of them represent focal hyperplasia in association with gastritis, rather than true neoplasms.

Adenoma. Adenomas of the stomach appear as sessile or pedunculated nodules, from a few millimeters to 2 cm. in diameter. They are firm, and contain abundant regular acinic spaces embedded in loose connective tissue. Malignant transformation at one or more foci is a frequent finding. A small percentage of carcinomas of the stomach are derived from an adenoma.

Multiple Polyposis. A particularly interesting but rare condition of the stomach is multiple polyposis. The entire mucosa is con-

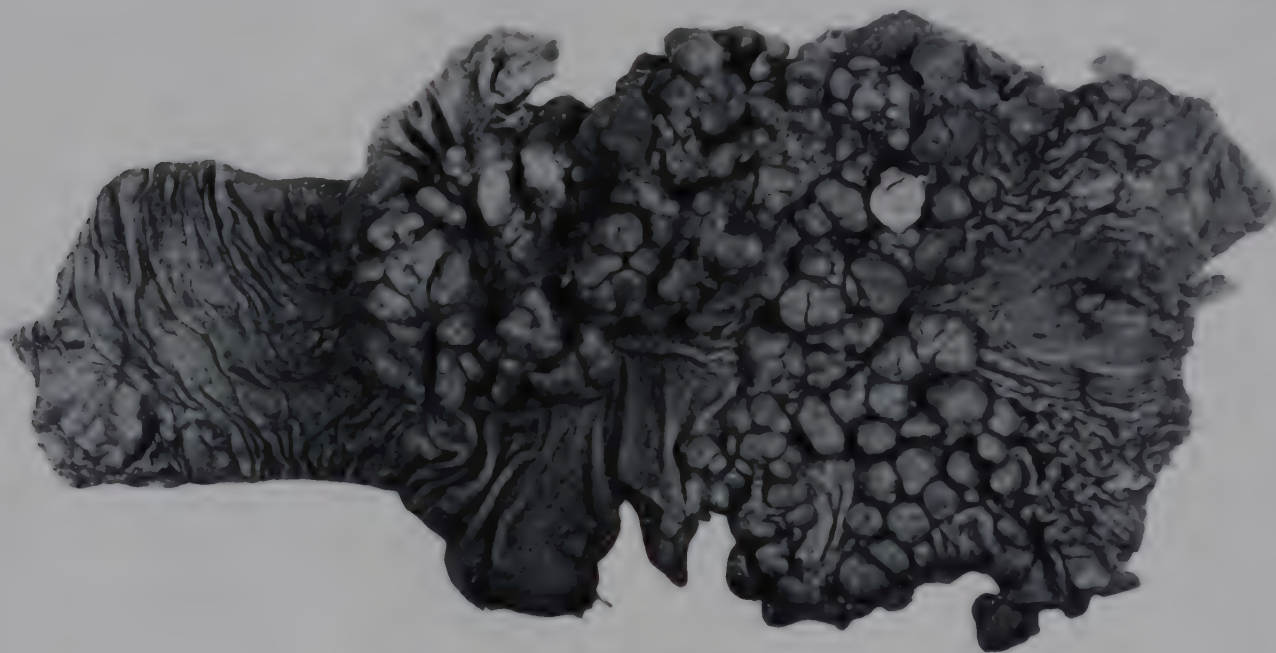


Fig. 321. Polyposis of stomach.

Benign Tumors of the Stomach

Leiomyoma. This is the commonest benign tumor of the stomach and constitutes about 60 per cent of the total. It occurs as a hard, smooth, round or lobulated tumor mass, varying in size from a few millimeters to 30 cm. in diameter. The smaller tumors are contained within the wall of the stomach, while the larger tumors project into the lumen or more commonly into the peritoneal cavity. On section they are seen to be composed of the typical whorled, interlacing bundles of pearly white tissue. Ulceration of the mucosa over the surface of the larger tumors is not uncommon. They occur in middle life, and occasionally undergo malignant transformation (Meissner).

Focal Hyperplasia. Small, single or multiple, sessile or pedunculated tumor masses similar to papillomas and polyps in other parts of the body have been described in the stom-

ach. It is probable that many of them represent focal hyperplasia in association with gastritis, rather than true neoplasms. The masses are covered by columnar epithelium and contain within them numerous glands. Ulceration is common, and malignant transformation has been reported (Pearl and Brunn).

Rarer tumors of the stomach include lipomas (Rumold), angiomas, fibromas, hemangiomas (Morton and Burger), and myxomas (Eliason and Wright).

Sarcoma of the Stomach

Pathologic Anatomy. Sarcoma of the stomach constitutes about 1 per cent of the malignant tumors of this organ. The most common type is lymphosarcoma, and fibrosarcoma and leiomyosarcoma follow in that order. They appear as small or large, usually encapsulated masses, within the wall of the stomach, or project beneath the serosa—exogastric. Lymphosarcoma not infrequently infiltrates the en-

tire wall and presents a picture similar to that of linitis plastica. The histologic details are essentially the same as in similar tumors in other organs. Metastases are first to the regional lymph nodes and then to the liver (Pack and McNeer).

Causal Factors. The fact that sarcoma of the stomach shows the same sex incidence (7:3 in men) as carcinoma of the stomach would suggest a similar causal factor. The average age is about forty-six years, which is ten years less than the average age of gastric carcinoma. There is no proved relation to peptic ulcer.

the uterus and breast. According to most statistics, gastric carcinoma accounts for from 30 to 40 per cent of all deaths from cancer.

Pathologic Anatomy. Gross Appearance. Most carcinomas of the stomach are of two types: ulcerating and vegetative. The former is a roughly circular mass 2 to 15 cm. in diameter, with elevated, firm, rolled edges and a central irregular crater. The vegetative type forms a large soft mass which projects into the lumen. Irregularly over the surface there are necrotic and ulcerated foci, and occasionally a papillary structure is discernible. On the cut section yellow or yellowish gray



Fig. 322. Carcinoma of stomach.

Clinicopathologic Correlation. Most sarcomas of the stomach either grow within the wall or project into the peritoneal cavity, and thus do not produce the high degree of obstruction which is seen in gastric carcinoma. Ulceration is rare, and hence hematemesis and melena are uncommon findings. The tumor may reach a large size and become adherent to surrounding structures. Occasionally a tumor along the greater curvature may invade between the two layers of the lesser omentum.

Carcinoma of the Stomach

In men carcinoma of the stomach is the most frequent malignant neoplasm, and in women it ranks second only to carcinoma of

foci embedded in a gray fibrillar stroma are seen. In the mucous membrane for a distance of several centimeters, small nonulcerated nodules—mucous membrane metastases—may be present. The architectural pattern of the wall is obscured. The mucosa and submucosa are fused into a single mass of neoplastic tissue. The normal mosaic of the muscularis is interrupted. The serosa is thickened, opaque, and grayish white; and frequently fine radiating white lines—permeated lymphatics—spread radially (Stout). In addition there is an infiltrative type in which the wall is uniformly thickened and indurated, frequently referred to as linitis plastica (Lapher and Parker).

Location. About 40 to 50 per cent of all

gastric carcinomas are on the lesser curvature side of the pyloric part of the stomach, and another 20 to 30 per cent along the lesser curvature. The others are on the greater curvature, anterior or posterior wall, and in the fundus—not over 10 per cent in any one part.

Extension and Metastases. Direct extension is observed from the fundus and greater curvature into the hilum of the spleen, and from the posterior wall into the pancreas. Extension from the lesser curvature into the liver is unusual. Metastases by embolism or permeation to the regional nodes in the lesser

It is frequently referred to as “Krukenberg’s tumor” (see p. 891).

Microscopic Appearance. Most carcinomas of the stomach are in the category designated as “carcinoma simplex.” There are small groups, sheets, or columns of cells without orientation to one another, arranged irregularly in a dense fibrous stroma. Only occasionally is there differentiation and orientation into acini. Many cells contain a small globule of mucus, and this sometimes is valuable in the identification of isolated neoplastic cells.

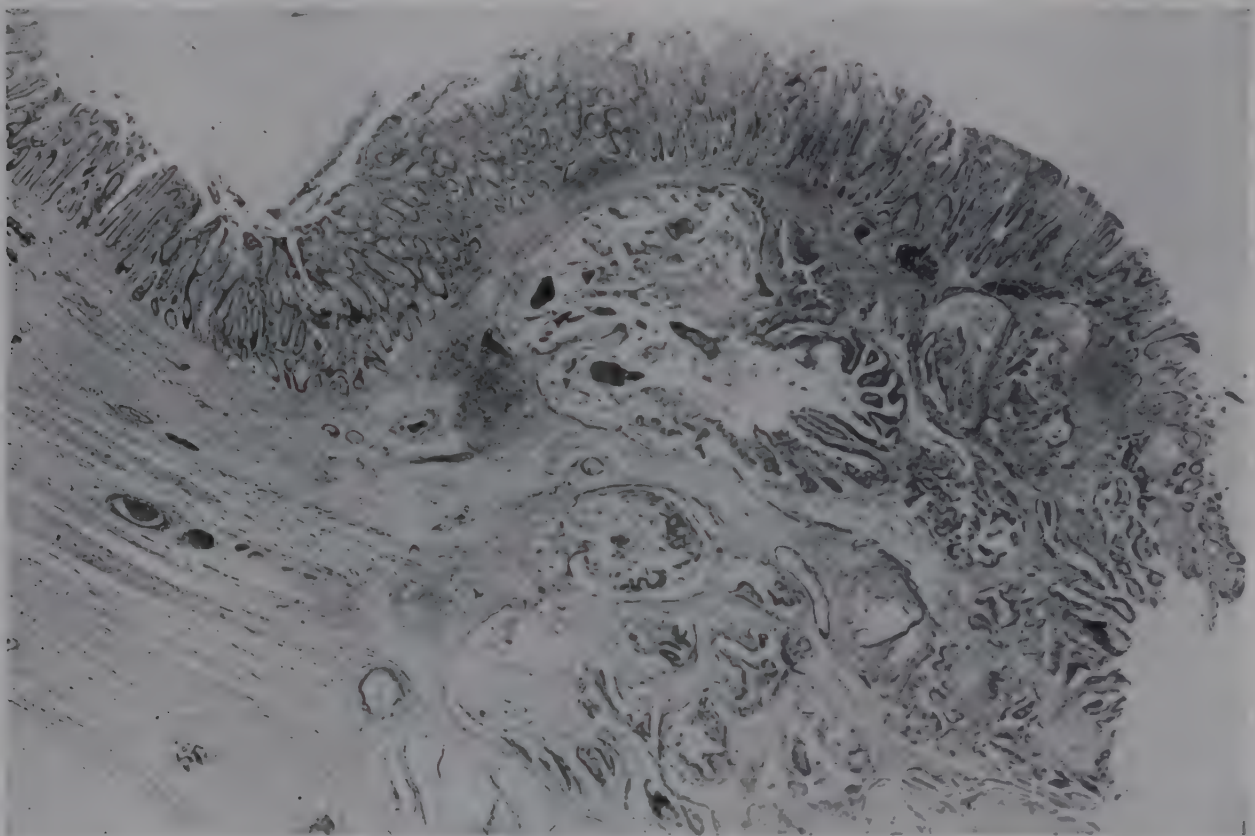


Fig. 323. Carcinoma of stomach showing junction of normal and neoplastic mucosa and growth of tumor under the adjacent tissue to form the elevated indurated margin.

omentum occur early. The nodes next to the stomach may not be involved first. At the time of death, metastases are present in the regional nodes and in the liver in about the same number—80 per cent.

VIRCHOW’S NODE. KRUKENBERG’S TUMOR. Two special types of metastases are important: the metastases to the left supraclavicular nodes (Virchow’s node, signal node), and those to the ovary. In most instances of advanced carcinoma of any abdominal organ, the thoracic duct is invaded, and embolism or permeation to the node near the orifice of the duct into the innominate vein is the basis for this clinically prominent metastases (Viacava and Pack). Metastases to the ovary is in most instances bilateral, and results from implantation of cells free in the peritoneal cavity.

Relation of Prognosis to Anatomic Structure. A good prognosis is related to sharp circumscription of the tumor, the presence of degenerative changes in the cells especially at the margin of the tumors, and an adenocarcinoma type (Steiner, Maimon, Palmer, and Kirsner).

Complications. Severe hemorrhage and perforation (Aird) occur but rarely in carcinoma. Perforation may go into the free peritoneal cavity, into a walled-off cavity, or into the colon.

Mucinous Carcinoma. Although the cells of almost all gastric carcinomas contain mucin, in only a few is it in sufficient amount to give the usual picture of a mucinous carcinoma growing as a vegetative mass into the lumen.

Incidence. Carcinoma of the stomach has

been reported in all decades, but over 70 per cent are in persons older than fifty years. There is a preponderance in men of 2:1.

Causal Factors. *Race.* In the Caucasian race, throughout Europe and America, carcinoma of the stomach occupies a predominant position in the total mortality from cancer. There are, however, differences in the various countries, as shown by Table 33, taken from the work of Cramer.

pathologic picture of chronic atrophic gastritis, and some believe that this lesion is the basis for the development of carcinoma in as high as 75 per cent of cases (Hurst). In general, most pathologists and clinicians have been reluctant to accept these observations, but the increasing use of the gastroscope has given further support to this conception (Schindler; Guiss and Stewart; Warren and Meissner). About 2 per cent of all patients

TABLE 33. GEOGRAPHICAL DISTRIBUTION OF GASTRIC CARCINOMA

Country	Total Mortality from Cancer per 100,000	Share of Gastric Cancer in Total Mortality in Percentage
England and Wales.....	118.0	22.2
United States.....	97.5	42.8
Holland.....	118.0	55.5
Sweden.....	120.0	60.5
Czechoslovakia.....	107.0	66.0

In the Orient, carcinoma of the stomach in Javanese is rare, while Chinese living in the same general environment show an incidence comparable to that in Europe (Bonne, Hartz, Klerks, Posthuma, Radsma, and Tjokronegoro). It has been assumed without proof that this difference in different countries and in different races is caused in part by constitutional differences and in part by dietary differences.

Economic Status. In general, carcinoma on the exposed parts of the body is more common in people of a low economic position, while carcinoma of the internal viscera is equally distributed throughout all social and economic classes. An exception to this is carcinoma of the upper alimentary canal in which the incidence increases with progressive decrease in the economic status of the individual. This is not true of carcinoma of the lower alimentary canal. It is possible that this exception results from defective alimentary hygiene—care of the teeth, character of the food, and regularity of eating (Cramer).

Occupation. No definite relation has ever been established between an occupation and carcinoma of the stomach, but in general the disease is commoner in rural than urban populations.

Chronic Atrophic Gastritis. In some examples of carcinoma of the stomach the remaining gastric mucosa shows the typical

with pernicious anemia develop carcinoma of the stomach—an incidence far in excess of that in the general population, indicating that there is some relation, as yet obscure, between these two conditions (Washburn and Rosendaal).

Heredity. There are a number of studies of families with a high incidence of carcinoma of the stomach, but these do not constitute more than a small percentage of all examples of the disease.

Peptic Ulcer. There can be no question that some carcinomas of the stomach start in pre-existing peptic ulcers. The subject has been fully discussed in the section on peptic ulcer (p. 654).

Adenomatous Polyps. Both single and multiple polyps of the stomach are rare, but, as in the colon, a significant percentage show histologic malignancy, and they must be considered precancerous lesions in a few instances of gastric carcinoma (Miller, Eliason, and Wright).

Clinicopathologic Correlation. Invasion of nerves is responsible for the earliest and most common symptom—pain. Ulceration is the basis for occult blood in the stool and in the gastric content. Long-continued bleeding leads to hypochromic anemia which is so characteristic of the disease. The invasion of the muscularis and the presence of a vegetative mass extending into the lumen act together to

mass) and focal absence of peristalsis (invasion of muscularis). The signs related to obstruction are conspicuous in tumors of the pyloric part that may be absent in fundal neoplasms, since the lumen in the latter is not seriously involved. The emaciation in advanced cases is the result of inadequate intake of food. In about half of the patients the mass is palpable. The usual achlorhydria or achylia is difficult to explain. Achlorhydria in turn the cause of the occasional diarrhea. Examination of gastric fluid for exfoliated tumor cells is a useful technique in diagnosis.

The average duration of life without treatment after the diagnosis is made is about twelve months. It is somewhat less in tumors of the lesser curvature and pylorus than of other parts, in men than in women, in patients with achlorhydria than in those with euchlorhydria or hyperchlorhydria, and in patients with serious anemia than in those with hemoglobin values above 70 per cent. Not more than 5 per cent of patients with carcinoma of the stomach are alive five years later.

Macrocytic Anemia in Carcinoma of the Stomach. Most carcinomas of the stomach ulcerate into the lumen, and bleeding results in a microcytic hypochromic anemia. On the other hand in cases in which the entire stomach is destroyed by carcinomatous tissue, a typical macrocytic hyperchromic anemia may develop. In these patients the gastric juice does not contain the intrinsic factor of Castle, but the anemia responds to administration of either the anti-anemic principle or the intrinsic factor (Goldhamer). Convincing proof of the definite relation of the pyloric part of the stomach to macrocytic anemia is given by the

small verrucae on the promontory is irregular, and in this there is atrophy.

In the literature nigricans are recorded as "juvenile" and "adult" is based on whether or not is present in some cases either at a distance of 1 cm. or more below the lesion. The relation between the lesion and the clear (Montgomery, Sidlick, and Ludy) has been reported in

Hypertrophic

Pathologic Anatomy

is thickening of the pylorus, so that it is as thick as normal abruptly at the base and fades off into the normal. There is thus a 1 cm. in length of the pylorus, and causing a 1 cm. diameter of the pylorus. The muscle is typically thickened, edematous, and there is no proliferation of fibers of the thickened muscle. The structure except for the size of muscle is normal. The result of pyloric obstruction is the wall is thickened and the obstruction may be at the agus. The small and contain little fat.

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develop in a small segment of the primitive
solid entodermal canal. The signs and symp-
toms are those of high intestinal obstruction,
with vomiting and absolute constipation.

Carcinoma of the Duodenum

Pathologic Anatomy. The duodenum is
rarely the seat of tumors. Of those which oc-
cur, the most common is carcinoma of the
major duodenal papilla. This appears as a rela-
tively small, firm, usually ulcerated mass 1 to
4 cm. in diameter, which destroys the papilla.
Carcinomas in the infrapapillary portions of
the duodenum are even rarer. They form local
ulcerating masses or annular tumors (Lieber,
Stewart, and Lund; Stewart and Lieber). All
these tumors are adenocarcinomas.

The secondary changes which result from
obstruction of the papilla are more important
than the direct effect of the carcinoma. As
the result of obstruction of the common bile
duct there is dilatation of the biliary system
and obstructive biliary cirrhosis in the liver.
In consequence of the obstruction of the pan-
creatic duct there is acinic atrophy of the pan-
creas and dilatation of the ductal system. Pene-
tration of the serosa brings about, in half of
the cases, peritoneal metastases (Lieber,
Stewart, and Lund).

Histogenesis. Since it is difficult to distin-
guish the several types of epithelium at the
major duodenal papilla (Baggenstoss), the
pathologist cannot determine the exact origin
of these tumors, and must designate them
collectively as "tumors of the major duodenal
papilla."

Causal Factors. There is no demonstrable
relation between duodenal ulcer and car-

vomiting, which is followed in time by loss of appetite, constipation, and emaciation. Ulceration into the duodenum results in occult blood in the stool. The obstruction of the common bile duct leads to jaundice, with all of the signs and symptoms dependent on the retention of the bile pigments and the bile salts in the blood and in the tissues. Obstruction of the pancreatic duct may produce steatorrhea.

Other Tumors of the Duodenum. All other tumors of the duodenum are extremely rare. Sarcoma of the ampulla of Vater has been reported (Moll). There are a few published examples of adenoma and papilloma of the ampulla, but the diagnosis of these are open to question (Baggenstoss). There is great doubt that melanoma is ever primary in the duodenum (Cooper).

Diverticula of the Duodenum

With possible rare exceptions, all diverticula of the duodenum are acquired and are of three types: those in the first part of the duodenum, those associated with the major and minor papillae, and those in the third part of the duodenum. They rarely produce clinical symptoms (Ackermann).

Diverticula of First Part. Diverticula within a few centimeters of the pylorus are almost always the result of a healed duodenal ulcer. During the active stage of the ulcer there is destruction of the mucosa and of the muscularis of the duodenal wall. After healing, this point is weak, and pressure from the duodenal contents will dilate it into a diverticulum. Not infrequently, these diverticula extend beneath the pyloric musculature and are directed toward the stomach.

Diverticula of Papillae. Diverticula associated with the duodenal papillae are often found if searched for carefully at operation or at autopsy. These diverticula measure from 2 to 4 cm. in length and 1 cm. in diameter. They are typically immediately adjacent to the point where the ducts perforate the duodenal wall, and are commoner at the major papilla than at the minor papilla. The cause is the same as in all pulsion diverticula—pressure from within against a weak place in the wall of a hollow viscus. In about 10 per cent the major papilla is carried into the diverticulum and opens into it. As almost all diverticula of the second part of the duodenum project

into the pancreas, it is possible that defective development of the longitudinal muscle from a misplaced piece of pancreas may be the basic cause for the weakening of the wall (Horton and Mueller).

Diverticula of Third Part. Diverticula in the third part of the duodenum are similar to those in the jejunum and ileum. They represent herniations of the mucosa and submucosa through a point in the muscularis, where the blood vessels pierce these structures.

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LXXXII

Diseases of the Intestine

From the standpoint of effective surface area for physiologic function, the small and large intestines constitute one of the larger organs of the body.

General Effects of Obstruction of the Upper Intestinal Tract. Acute Dilatation of the Stomach

In sharp contrast to the mild effects of partial or complete obstruction of the colon, occlusion of the lumen of the duodenum or of the upper jejunum results in profound clinical and pathologic changes, and in death unless the cause of the obstruction is promptly removed. The suddenness of onset and the severity of the symptoms are in direct proportion to the height of the obstruction, those in the duodenum producing the most advanced changes. At autopsy the pathologic changes, except for hyperemia of the viscera and intense hyperemia and edema of the mucosa of the duodenum, are inconspicuous.

Chemicophysiologic Aspects. In animals a clinical syndrome identical with that in man can be produced by obstruction of the duodenum or by the injection of the contents of a closed duodenal loop which has remained in the body for two or three days. The causal agent is clearly some substance produced by the mucosa of the small intestine, since the syndrome does not result when the mucosa is destroyed by sodium fluoride (Whipple, Stone, and Bernheim). The toxic agent has been partially purified and is believed to be a proteose (McQuarrie and Whipple).

Acute Dilatation of the Stomach. In a variety of conditions, notably following operations, acute dilatation of the stomach and a clinical syndrome not unlike that of high intestinal obstruction may result. There are few definite pathologic changes, and it must be

supposed that the disease is based upon some functional disorder. The most plausible theory is that there is a primary paralysis of the musculature of the stomach, followed by an accumulation of fluid. The distended stomach presses the intestines into the pelvis and thus drags upon the superior mesenteric artery at the root of the mesentery. This in turn brings about partial compression of the third part of the duodenum (Borchgrevink). Acute dilatation of the stomach in its later phases then becomes the equivalent of high intestinal obstruction. A plausible explanation of the tremendous amount of fluid which accumulates in the stomach is that it represents the sum total of gastric and duodenal secretion under the influence of an increased elaboration of secretin (Dragstedt and Dragstedt).

Clinicopathologic Correlation. The outstanding symptoms of high intestinal obstruction and of acute dilatation of the stomach are distention of the abdomen, pain, and vomiting. They depend in part upon the actual obstruction and in part on the absorption of toxic materials. The systemic symptoms of collapse are the result of the toxic principle elaborated in the obstructed loop of intestine. These symptoms and signs are in large part the result of a change in capillary permeability, so that fluid is lost into the tissues with resulting hemoconcentration. Therapy must be directed toward correcting this defect.

Causes and Effects of Intestinal Obstruction—Ileus

Intestinal obstruction or ileus—a failure of onward flow in the intestinal lumen—is an important primary and secondary cause of death.

Types and Causes. One of the most satisfactory classifications of intestinal obstruc-

tion is that of Wangensteen. The percentage figures for each type are taken from the paper by Vick.

- I. Mechanical obstruction (dynamic)
 - A. Narrowing of the lumen
 1. Stricture (atresia, inflammatory, neoplastic) (15 per cent)
 2. Obturation (foreign bodies) (1 per cent)
 3. Compression from without
 - B. Obstruction from adhesions or bands (18 per cent)
 - C. Hernia (47 per cent)
 - D. Volvulus (2.5 per cent)
 - E. Intussusception (15 per cent)
 - F. Developmental anomalies
- II. Obstruction caused by nervous imbalance (adynamic)
- III. Obstruction caused by vascular disturbances.

Effects. The general effects of obstruction of the intestine depend on: the location of the obstruction, the rapidity of onset of the obstruction, the presence or absence of associated vascular disturbances, and the development of a closed loop of intestine. From the therapeutic viewpoint, mechanical (dynamic) as opposed to paralytic (adynamic) causes must also be considered.

Paralytic Ileus. The type of intestinal obstruction caused by inadequate or absent intestinal motility is called "paralytic," "adynamic," or "inhibition" ileus. It may be the result of intra-abdominal conditions such as peritoneal irritation in peritonitis, or of extra-abdominal diseases such as severe infections, uremia, and lesions of the spinal cord (Ochsner and Gage).

Pathologic Anatomy. The entire bowel is usually involved and the intestine greatly dilated. The lumen is filled with liquid and gas, and the wall is thin. Other changes are not characteristic and vary with the primary disease. At first the accumulation is directly related to the obstruction, but later a vicious circle is established. The dilatation leads to stimulation of secretion and inhibition of absorption and progressive increase of distention.

Clinicopathologic Correlation. The clinicopathologic correlation does not differ from that of other types of intestinal obstruction except in one respect: the absence of peristalsis as determined by inspection, palpation, and auscultation.

Foreign Bodies in the Intestine— Obturation Obstruction

Any of the foreign bodies found in the esophagus and stomach may be present in the intestine: gallstones, bezoars, metal trinkets, pins, or false teeth. In addition, masses of parasites and concretions of the content (fecaliths and enteroliths) must be considered (Storck, Rothschild and Ochsner).

Gallstone Ileus. The commonest and most important type of obturation obstruction is that caused by a gallstone. It occurs in about 0.3 per cent of all instances of cholelithiasis. Although a stone which reaches the intestine through the ducts and ampulli may cause obstruction, the usual mechanism is discharge of a large stone through a cholecysto-enteric fistula, usually into the duodenum. The most frequent site of impaction is the terminal ileum. The patient is usually an older woman who has had symptoms of biliary disease for many years (Foss and Summers).

Foreign Bodies in the Rectum. Many objects may be introduced intentionally or accidentally into the rectum: thermometers, bottles, syringe nozzles, etc. (Drueck).

Perforation of the Intestine. Foreign bodies in the lumen may perforate the wall. Other causes of rupture and increase of intraluminal pressure are enemas (Hawkes) and injections of air, nonpenetrating trauma to the abdomen as in water blast (Auster and Willard); and injury to the wall by instruments (Crohn and Rosenak).

Meckel's Diverticulum

The commonest anomaly of the omphalomesenteric duct is a persistence of the proximal end as a small evagination of the intestine known as "Meckel's diverticulum." It is located most frequently at a point on the antemesenteric border of the ileum, about 100 cm. above the ileocecal valve. The average length is from 3 to 5 cm. and the average diameter approximately 1 to 2 cm., but diverticula up to 15 or 20 cm. in length have been reported. The diverticulum is typically lined with the mucosa of the lumen, but from 15 to 20 per cent contain islands of jejunal or duodenal mucosa, and an additional 15 to 20 per cent contain islands of gastric mucosa. A small

nodule of pancreatic tissue, especially in the tip of the diverticulum, is a not uncommon finding.

The mere existence of an evagination of the intestine is rarely of clinical significance. On the other hand, secondary changes or diseases of this structure are responsible for a certain percentage of acute intra-abdominal conditions. Thus the diverticulum may serve as the starting point for an intussusception of the small intestine (Harkins). A peptic ulcer located near the orifice of the diverticulum is one of the causes of intestinal bleeding, and may perforate into the peritoneal cavity. In most cases of peptic ulcer near Meckel's diverticulum, the entire diverticulum has been lined with gastric mucosa, furnishing additional proof of the importance of gastric juice in the genesis of ulcers (Aschner and Karelitz). Tumors, specifically myomas, sarcomas, carcinoids, and carcinomas, may arise within the tissues of Meckel's diverticulum (Costich and McNamara).

Diverticula of the Small Intestine

Pathologic Anatomy. Aside from Meckel's diverticulum, diverticula of the small intestine occur almost exclusively in the upper jejunum, and are found as thin-walled cavities, 1 to 5 mm. in diameter, between the leaves of the mesentery. They are usually multiple and are filled with fluid or gas. The wall is composed of peritoneum, mucosa, and submucosa, without a muscular layer. By careful examination, an artery may be demonstrated perforating the circular muscle at the point where the diverticulum connects with the intestine (Fraser).

Causal Factors. This type of diverticulum is found in older persons and is caused by an increased intra-intestinal pressure, acting on the weakest point of the intestinal wall. This point is where the mesentery attaches, since here the longitudinal muscle is relatively thin and the arteries to the submucosa and the mucosa perforate the circular muscle.

Clinicopathologic Correlation. Signs and symptoms are absent or indefinite. The diverticula are not uncommonly observed in routine x-ray examinations (Case).

Duplication of the Gastro-intestinal Tract. Rarely, small or large cystic cavities are found

in the wall of the intestine or stomach or within the leaves of the mesentery. These cavities are lined with gastric, ileal, or colonic mucosa, and represent small pieces of the primitive gut which have become separated from the main lumen. Occasionally, the cavities communicate with the intestine or stomach and have been termed "giant diverticula," or "double stomachs" and "double intestines." They should not be confused with enteric cysts derived from the omphalomesenteric duct (Bremer).

Celiac Syndrome

What is frequently referred to as celiac disease is in fact a syndrome characterized by emaciation, distention of the abdomen, bulky foul smelling frothy stools that contain excessive fat, and frequently retardation of growth.

From the standpoint of pathologic anatomy this syndrome may be classified into two types: primary or idiopathic and secondary. In the primary or idiopathic there are no demonstrable anatomic lesions which may be considered characteristic or causal. The secondary type occurs in a variety of conditions: congenital malformation of the intestine or its attachments, chronic infections, dysentery, megacolon, and a distinctive type of disease involving the pancreas and other organs. Each of these diseases is described elsewhere except the last which will be described in this section under the name of infantile pancreatic insufficiency.

Infantile Pancreatic Insufficiency. Other names which have been applied to this disease are congenital pancreatic steatorrhea and cystic fibrosis of the pancreas.

Pathologic Anatomy. The pancreas appears small and firm. The ducts are irregularly dilated to form small cystic spaces filled with fluid or inspissated secretion. Extensive fibrosis and replacement of the acinic tissue is seen microscopically. In many of the ducts there is squamous metaplasia. In the lungs the findings vary from acute bronchopneumonia to chronic bronchiectasis with abscess formation. In some cases intracytoplasmic inclusion bodies similar to those of the salivary gland virus may be found in the lung and in the pancreas.

In a few patients the small intestine is greatly distended with thick viscid mucosa, a condition known as meconium ileus. The glands of the mucosa are distended with inspissated secretion. Rarely the liver is involved and obstruction by the thick secretion leads to obstructive biliary cirrhosis (Farber).

Manifestly this condition is a systemic disease and not just one of the pancreas. The common lesion is an increase in viscosity of the secretions of glands. It occasionally occurs in several children of the same family.

cecum and even the colon as far as the sigmoid show similar changes. Occasionally, segmental parts of the ileum are affected with relatively normal intestine between.

The most characteristic histologic features are extreme edema of the submucosa and hyperplasia of the lymphoid tissue of submucosa and regional nodes. In the involved lymphoid tissue tubercles or isolated giant cells occur frequently. With chronicity there is fibrosis. The muscularis is infiltrated but not hypertrophic (Hadfield).

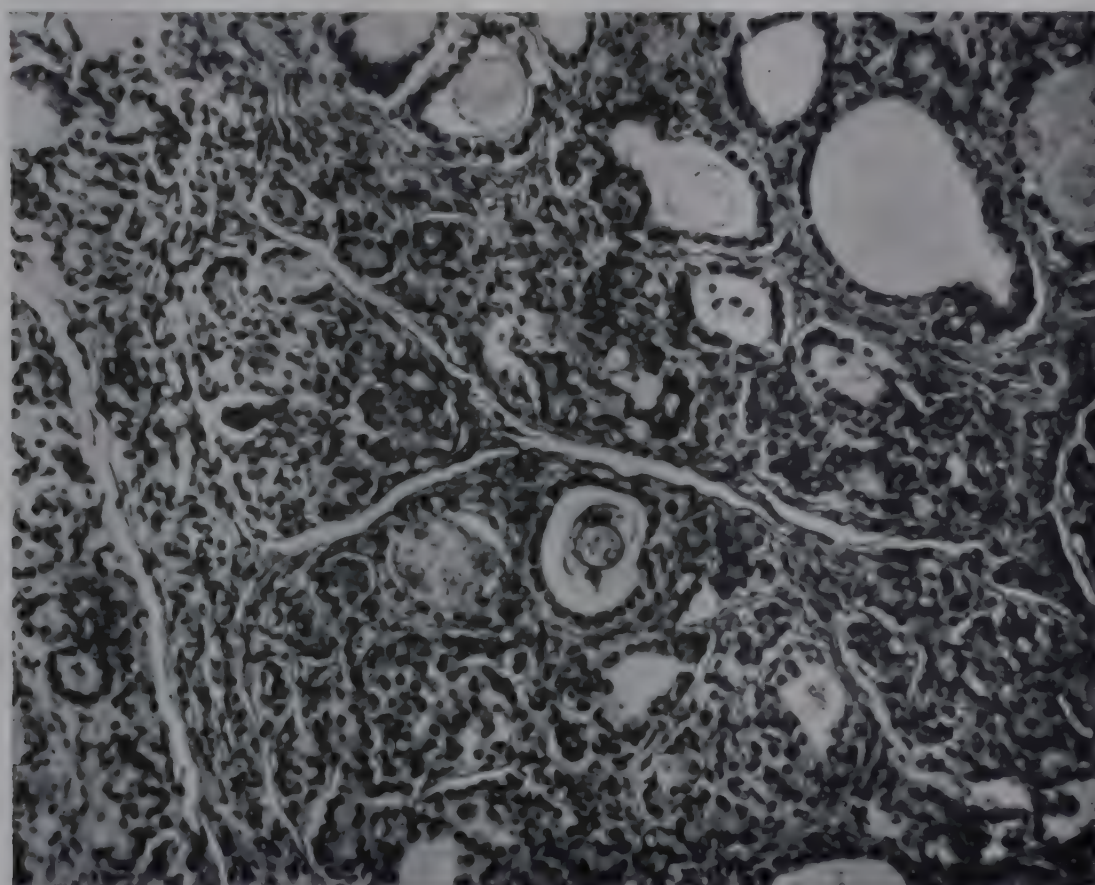


Fig. 324. Pancreatic fibrosis in a child with infantile pancreatic insufficiency.

Regional Enteritis and Enterocolitis

This condition, also known as “regional” or “segmental” ileitis, “terminal” ileitis, and “chronic cicatrizing” ileitis or enteritis, was first described by Crohn, Ginzburg, and Oppenheimer in 1932.

Pathologic Anatomy. The typical lesion is in the terminal ileum. The wall is thickened and firm, and the serosa partly covered by prolongations of the mesenteric fat. The lumen is decreased in size, and the mucosa is thickened and ulcerated. Fistulas may extend from the ulcers into other loops or into the mesentery, which is thickened and indurated. The mesenteric nodes are enlarged. Beyond the severely involved regions the deposits of serosal fat and mucosal ulceration are present and in general coexistent. Less commonly, the

Incidence. Most patients are between twenty and forty years of age. The two sexes are equally affected, but there seems to be a high incidence in Jewish persons. Occurrence in families and in those of high economic groups is rare. The incidence is apparently increasing (Shapiro).

Causal Factors. The lesions are similar to those of tuberculosis, but all attempts to demonstrate the tubercle bacillus have failed. There is also a resemblance to sarcoidosis (Homans and Hass). The primary involvement of the lymphoid tissue and the lymphedema of the submucosa suggests an initial lesion of the wall rather than of the mucosa. The occurrence of regional enteritis after bacillary dysentery has been used as evidence of a causal relation (Felsen).

Clinicopathologic Correlation. Disturbances

of intestinal motility result in diarrhea and cramping pain, ulceration accounts for the melena, the thickened, matted intestine is the basis of the mass in the lower abdomen, the stenosis of the lumen gives rise to intestinal obstruction, infection produces the fever, and inadequate absorption causes the emaciation and avitaminoses.

Surgical treatment by resection has been successful: operative mortality is 9 per cent, and there is recurrence in about 10 per cent.

is more frequent in men in a ratio of 3:2. The onset is sudden and marked by signs of peritoneal irritation and intestinal obstruction. Even with prompt surgical treatment, the mortality may reach 75 per cent (McClenahan and Fisher).

Miscellaneous Lesions. Infarcts of the omentum (Lipsett) and of the appendices epiploicae (Eliason and Johnson) may be caused by torsion. Infarcts of the omentum may be segmental (Pines and Rabinovitch). Rupture

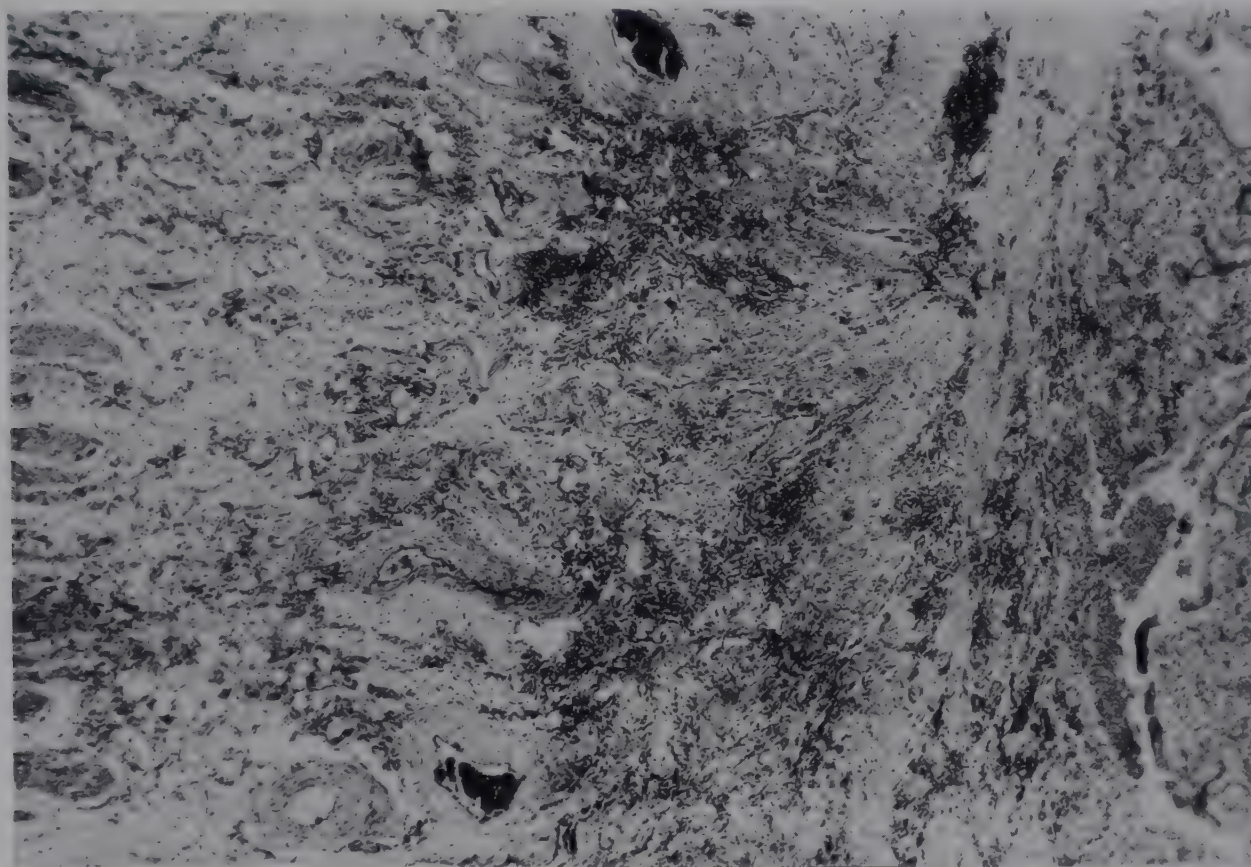


Fig. 325. Regional enteritis. Muscularis on the left and mucosa on the right.

Mesenteric Vascular Occlusion— Infarct of Intestine

Pathologic Anatomy. Occlusion of the vessels supplying the intestines is most frequent in the superior mesenteric system (90 per cent) and in the arteries (60 per cent). The vessel usually is the seat of moderate arteriosclerosis, and the obturation is caused by a thrombus.

Soon after vascular occlusion the intestine becomes dark red and then deep purple. The serosa is dull and frequently covered by a fine fibrinous exudate. With the passage of time, the wall increases in thickness, largely because of edema and hemorrhage. The mucosa undergoes autolysis, and finally the entire wall changes into a friable, dark-red, soft tissue.

Clinicopathologic Correlation. The condition is rarely seen in persons under forty, and

of an arteriosclerotic mesenteric vessel with hemorrhage—intra-abdominal apoplexy—has been reported (Morton).

Intussusception

Pathologic Anatomy. Intussusception is a telescoping of a segment of the bowel into the immediately adjacent, usually distal segment. In cross-section three (or six if both sides are counted) complete layers of the intestinal wall are seen. On the outside is the sheath or intussusciens, with the mucosa directed lumenward; next is the middle or returning layer, with the mucosa apposed to that of the sheath; and innermost is the entering layer, with the peritoneum in contact with the peritoneum of the returning layer. The intussusception carries the mesentery in, and there usually results tension on and partial or com-

plete occlusion of the vessels. The inevitable result is first congestion, edema, and hemorrhage, and finally infarction of the intussusceptum (Iason).

Causal Factors and Pathogenesis. It is probable that the precipitating factor in intussusception is a local persistent contraction of the intestine, so that the following peristaltic wave pushes the upper intestine into the lower. In children—and over 80 per cent of all examples are in children less than two years of age—there is usually no evident cause. In most instances in adults, a focal lesion—accessory pancreas, diverticulum, benign or malignant tumor—is present at the apex of the intussusceptum.

Clinicopathologic Correlation. The mass of tissue at one point is usually palpable as an ovoid or cylindrical tumor in the abdomen. The intussusceptum partially fills the lumen and causes intestinal obstruction. Disturbances of blood supply lead to hemorrhage, ulceration of the mucosa, and hence blood in the stool. The mortality varies directly with promptness of surgical treatment: 10 per cent if there were symptoms for twelve hours and 60 per cent after seventy-four hours (Ladd and Gross).

Postmortem Intussusception. In some autopsies, especially on children, small multiple intussusceptions may be present. They are to be distinguished from the antemortem type by the ease of reduction and the absence of pathologic change in intussusceptum.

Volvulus

Pathologic Anatomy. Volvulus, a twisting or kinking of the intestine around the long axis, occurs most frequently in the sigmoid and in the small intestine. With complete occlusion at both ends of the twist, the wall is thin and the lumen greatly distended with liquid. Interruption of blood supply results in the pathologic changes described under "Mesenteric Vascular Occlusion," p. 671. In lesser degrees of volvulus the veins only are occluded, and the intestinal wall is edematous and dark red. Frequently, the peritoneum is covered by a fibrinous exudate, or there is a generalized peritonitis.

Causal Factors and Pathogenesis. Any lesion which brings about a lengthening of the intestine or a narrowing of the mesentery may

be a predisposing cause. The precipitating causes are unequal distribution of weight, as in a large fecal mass at one point in the sigmoid, and active peristalsis. The incidence is higher in men (3:1) and in those over forty years.

Clinicopathologic Correlation. Slight thickening of the mesentery and peritoneum of the involved part, and the frequent history of self-limited previous attacks, indicate that volvulus occurs repeatedly in those predisposed to it. The signs and symptoms are related to obstruction of the intestine (see p. 667), to vascular occlusion and infarction (see p. 671), and to the peritonitis sequential to both (see p. 295). The rapidity of onset and severity vary with the extent of rotation (90 to 360 degrees) and with the degree of vascular disturbance. Even with good medical and surgical care the mortality is about 40 per cent (McKechnie and Priestley).

Tumors of the Small Intestine

Both benign and malignant tumors of the small intestine are rare, and of those which occur the commonest is the duodenum and ileum. Duodenal tumors are discussed elsewhere (p. 663).

Benign Tumors. Most benign tumors are spherical, solitary or multiple, and submucosal, intramural, or subserosal. The center of the larger neoplasms frequently undergoes necrosis, and may discharge into the lumen. The histologic structure does not differ from that of similar tumors in other locations. In order of frequency they are: adenoma, leiomyoma (Smith), fibroma (Moore and Schmeisser), lipoma (Comfort), hemangioma (Ackerman), and neurogenic fibroma (Stout). The carcinoid is discussed with tumors of the peripheral nervous system (p. 962).

Carcinoma. The usual carcinoma of the small intestine is an annular ulcerated adenocarcinoma (Boman).

Sarcoma. The important malignant mesenchymal neoplasms are the leiomyosarcoma and the lymphosarcoma. The former is a localized mass, while the latter causes a diffuse infiltration of the wall with a grayish white, granular, friable tissue (Usher and Dixon).

Clinicopathologic Correlation. Most benign tumors of the small intestine are incidental

and produce no symptoms. Of those with clinical change there are three basic mechanisms: focal irritation and induction of an intussusception; ulceration into the lumen with blood in the stool; and growth within the lumen resulting in obstruction. Only a few are large enough to palpate. The life expectancy with a malignant tumor is rarely over a year.

Hernia

A hernia is a protrusion of a viscus through the wall of the cavity in which it is normally contained. The lining of the cavity is pushed ahead of the viscus as a sac. Two causal factors must be assumed in the genesis of hernias: increased pressure within the cavity, and a focal weakness of the wall. The latter is the determining factor in localization.

Peritoneal Hernia. The congenitally weak points of the peritoneal wall are: the inguinal canal through which the testis passes during descent (indirect inguinal hernia), the triangle of Hesselbach (direct inguinal hernia), the region through which the femoral vessels enter the leg (femoral hernia), the region of the umbilicus (umbilical hernia), and the diaphragmatic hiatus for the esophagus and aorta (diaphragmatic hernia). Acquired hernias result from the trauma of childbirth on the perineum (perineal hernia) or from healed wounds of the anterior abdominal wall (ventral hernia). A sliding hernia is one in which one wall of the sac is the normal peritoneal attachment of that segment of intestine (Stephens, Moore, Brown).

Any of the normally weak points may be widely patent at birth and show a hernia at that time or within a few days or weeks. In other persons the tissue is only partially defective, and trauma in connection with physical labor such as lifting (which also increases intra-abdominal pressure) may initiate the protrusion of a sac.

Intra-abdominal Hernia. In addition to the hernia appearing on the surface of the body, there is a group of similar conditions within the peritoneal cavity. Lesions about the diaphragm have already been discussed (p. 648). There remain (1) those which occur in normal pockets such as the foramen of Winslow, and into the periduodenal, pericecal, and intersigmoidal fossae; (2) those occurring in

evaginations of normal mesenteric folds, such as in the broad ligament; (3) those associated with traumatic or operative bands or adhesions, and (4) those related to fibrous adhesions dependent on chronic or healed inflammation. In the first two groups, the same causal factors are operative as with all other hernias. These hernias have a sac. Strictly speaking, the latter two groups are not hernias, because there is no sac. A segment of the intestine is caught beneath an adhesion, but it is still free within the peritoneal cavity (Mayo, Stalker, and Milier).

Complications. As long as the viscus, usually intestine, contained in a sac is free to move in and out, the hernia is reducible, and there are no symptoms except those of a mass. If the viscus is trapped in a large sac with a narrow orifice, or if chronic inflammation forms adhesions to the sac, the hernia becomes irreducible. If there is inflammatory swelling or kinking of the intestine, the hernia is designated as "incarcerated." The signs and symptoms are those of intestinal obstruction. The most serious complication is impairment of blood supply and infarction of the herniated intestine—strangulated hernia (Douglas). The result is the same as that described under mesenteric thrombosis (p. 671).

Visceroptosis

The position of the abdominal viscera depends on the general bodily configuration; thus in tall, slender people the stomach is long and extends as far as 13 cm. below the interiliac line into the true pelvis. In broad, robust people the stomach is more transverse in position and does not extend into the pelvis (Moody, Van Nuys, and Chamberlain). When these factors are taken into consideration, a diagnosis of true visceroptosis is practically never made.

Anomalies of the Colon

During development the colon rotates completely, and the cecum descends from a position just beneath the liver to the normal location in the lower quadrant. Rotation may fail, the cecum may not descend, or the cecum may descend too far into the pelvis. As the colon reaches the normal position, parts of the cecum and ascending colon and descending colon become relatively fixed. Lack of fixa-

tion and too firm fixation are occasionally the cause of indefinite symptoms. Rarely, the small intestine and colon have a common mesentery (Kantor). Duplication and triplication of the colon have been reported (Gray).

Primary Megacolon

In contrast with dilatation of the colon secondary to obstructive lesions, there is a type which is apparently primary. In children it is called "Hirschsprung's disease" (Hurst).

Pathologic Anatomy. The most conspicuous changes are in the rectosigmoid. The lumen is enormously dilated: reports of circumferences up to 100 cm. and fecal masses weighing 50 pounds have been made. The wall is greatly thickened and firm. The muscularis, chiefly the circular layer, is hypertrophic. The mucosa is thick, vascular, edematous, and sometimes ulcerated. The muscularis mucosa is hypertrophic. The mesenteric nodes are enlarged and hyperplastic. In a cephalad direction the lesions become less marked, and frequently end abruptly in the descending colon, or rarely as high as the ileocecal valve.

Incidence and Causal Factors. Primary megacolon is a rare disease, most common in boys under one year of age, but seen at all ages. The cause is unknown, but some deficiency of the sacral parasympathetic innervation of the distal colon seems likely (Law).

Clinicopathologic Correlation. The accumulation of intestinal contents obviously leads to constipation and infrequency of bowel movements—as long as months apart. The dilatation results in distention of the abdomen, eventration of the diaphragm, and discomfort. The radiograph shows the marked dilatation and obliteration of the haustral markings.

The prognosis is poor in young children: 85 per cent die before the fourth year. In older children and adults there is little effect on life expectancy. The direct complications include volvulus and fecal impaction.

Functional Disorders of the Colon

Colonic Neuroses. A colonic neurosis is an intermittent or constant disturbance of colonic function which cannot be ascribed to an organic or non-neurogenic disorder, and which seems dependent upon a derangement of the autonomic innervation of the colon (Bockus).

Two types are recognized: a motor type (spastic or irritable colon); and a secretory type (mucous colitis).

Anatomic studies show little change. There is typically no inflammation, although in the active secretory stage there may be hyperemia and slight edema. The mucosal glands are distended with mucus.

Postulated causes include imbalance of the autonomic system, psychogenic factors, endocrine factors, allergy, and bacterial infections. It is commonest in persons between twenty and fifty, with a slight preponderance in women.

Constipation. Constipation is an undue delay in the discharge of, or the abnormal retention of, the intestinal contents. In addition to the manifold organic lesions causing retention, there is a type referred to as "simple constipation." Hurst recognized two basic varieties: colonic constipation, in which the passage of the contents along the colon is abnormally slow, and dyschezia, in which defecation is inefficient. The causes are not well understood but include poor dietary habits, abuse with laxatives, weakness of the abdominal and pelvic muscles, deficient reflex activity of the intestine, and hyperacidity in the stomach.

Diarrhea. The causes of diarrhea (to be differentiated from dysentery) are manifold. Bockus lists achylia and preceding gastroenterostomy, diseases of the intestine, functional colonopathies, defects in absorption, pancreatic disease, cholecystic disease, diarrhea of nervous origin, and systemic disease (nephritis, diabetes, allergic states, hyperthyroidism, and amyloidosis).

Chronic Ulcerative Colitis

Pathologic Anatomy. The typical lesions of chronic ulcerative colitis are more abundant and more advanced in the rectum than in any other part of the colon, but in some cases the entire colon, ileum, and jejunum may be uniformly involved. The single ulcers extend to or through the muscularis and are arranged linearly directly under the taenia. The wall of the intestine is thickened and firm, and the lumen may be decreased in size, either diffusely or focally as the result of the cicatrization. The single ulcers become progressively confluent, leaving only small foci of

the mucosa, which project above the surface of the beds of the ulcers. These small masses of mucosa are edematous, and the few glands which remain are completely devoid of goblet cells. The veins in the wall of the intestine and in the adjacent mesentery may contain either bland or infected thrombi. The base of the ulcer is formed by connective tissue, heavily infiltrated with lymphocytes and mononuclear cells. The edges are slightly undermined. The serosa is thickened by fibrosis (Warren and Sommers).

Complications. The most common complications of chronic ulcerative colitis are perforation of the colon with peritonitis, and perforation of the rectum with the formation of fistulas and perirectal abscesses. Less com-

of the intestinal musculature. More persuasive are the observations of Lium and Porter, who associated the ulcerations with spasm of the taenia. The allergic theory lacks definite support. In the matter of deficiency states it is difficult to separate cause and effect. The more severe the ulceration and the more extensive the disease in the small intestine, the more likely there will be evidences of vitamin or nitrogen deficiency.

Clinicopathologic Correlation. The extensive ulceration of the colon leads to irritability of its musculature, and consequent dysentery and diarrhea, with pain from the intense muscular contraction. Through the ulcers, by the exudation of plasma and hemorrhage, considerable amounts of nitrogen are lost, so

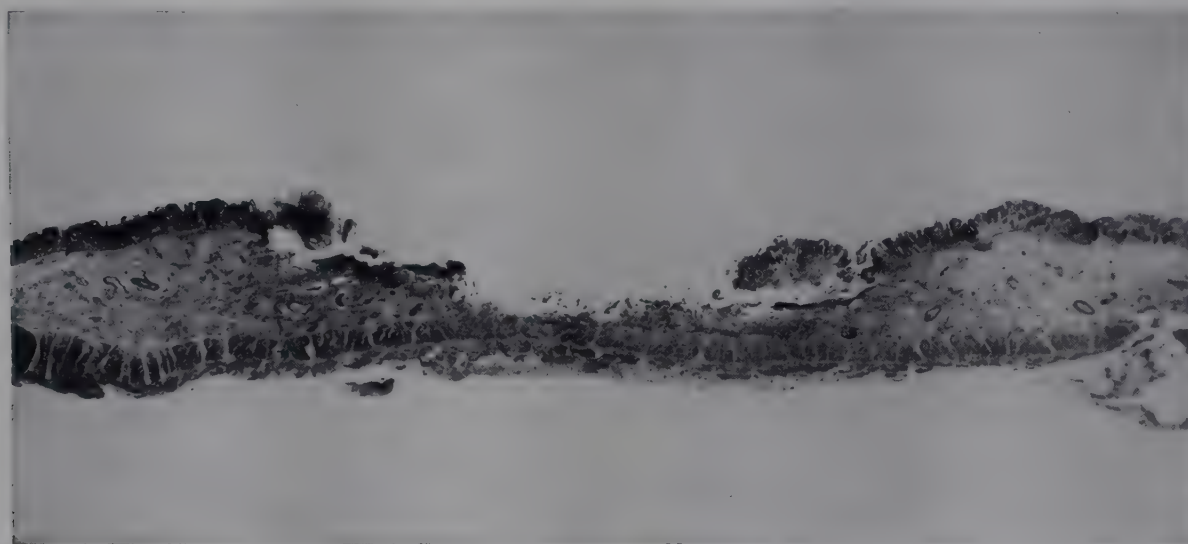


Fig. 326. Chronic ulcerative colitis.

mon are pylephlebitis with multiple abscesses in the liver, infection of the urinary tract, and septicemia. Carcinoma of the colon develops in about 4 per cent.

Incidence. The average age of onset of chronic ulcerative colitis is about thirty, and it occurs in the two sexes with about equal frequency.

Causal Factors. There are four basic concepts concerning the cause: the bacterial, neurogenic, allergic, and deficiency theories. Among the bacteria which have been incriminated, the dysentery bacillus, the diplostrep-tococcus of Bergen, and the *Bacterium necrophorum* of Dack and his coworkers are the most prominent. Conclusive proof that any one of them is the cause has not yet been submitted. The neurogenic theory is based upon the observed emotional instability of the patients. It is supposed that there is a relation between emotional upsets and hyperactivity

that there is an increased excretion of nitrogen in the feces, a decreased excretion of nitrogen in the urine, and a low level of blood urea (Welch, Adams, and Wakefield). The hemorrhage leads to varying degrees of hypochromic anemia.

Gangrenous Pyoderma. Rarely in association with other diseases, and usually in association with chronic ulcerative colitis, a peculiar infection of the skin develops, known as "gangrenous pyoderma." Grossly, the lesions are discrete or confluent ulcerations of the skin of the extremities and of the thorax, with small abscesses. *Staphylococcus albus* and *Streptococcus haemolyticus* may be isolated from the pus.

Diverticula of the Colon

Pathologic Anatomy. Diverticula of the colon are commonest in the sigmoid, and de-

crease in incidence toward the cecum and rectum. The usual site is between the mesocolic and antimesenteric taenias. The diverticula average 5 to 7 mm. in diameter. From the outside they appear as spherical or pyriform blue-black masses, attached to the intestine and frequently covered by excessive amounts of fat. From the inside the orifice is seen as a small circle or slit, 1 to 3 mm. in diameter. By pressure on the diverticulum a firm mass of feces may be expressed from most. The wall is composed of the mucosa, submucosa, and serosa. The muscularis may cover the neck for a short distance, and rarely



Fig. 327. Diverticula of the colon. (Radiograph by courtesy of Dr. Sherwood Moore.)

an occasional muscle fiber is present over the convexity (Mailer).

Diverticulitis. Most diverticula show no evidence of inflammation, but, if the mucosa is penetrated, a type of reaction similar to that of appendicitis is established, especially if the orifice is occluded by feces or by edema. The inflammation may be acute or chronic, and may spread in the surrounding tissue as peridiverticulitis. Perforation is usually limited, and a peridiverticular abscess is formed. Occasionally, perforation is into the free peritoneal cavity, and peritonitis results. Rarely, a fistula to the genital tract is established: about half of all vesicocolic fistulas are on this basis (Higgins).

Causal Factors. Incidence. Colonic diverticula are predominantly lesions of obese, constipated persons over forty years of age. The reasons for this are not entirely clear. Obesity weakens the abdominal wall and impairs the intra-abdominal tension. Further, fat infiltration about the colon separates the muscle fibers and weakens the wall. Constipation undoubtedly leads to increase of intraluminal pressure.

In routine radiographic examination by barium enema of persons over forty, diverticula are observed in about 6 per cent, while careful anatomic study may show as many as 20 per cent.

Clinicopathologic Correlation. About one-half of persons with diverticula have symptoms referable to their presence—diarrhea, constipation, epigastric distress, etc. (Willard and Bockus). The clinical relations of diverticulitis are reflected in the colloquial synonym “left-sided appendicitis” (Hayden).

Solitary Cecal Diverticulum. This is a distinctive lesion, apparently not causally related to the usual type. Peridiverticulitis and abscess formation is the usual fate (Jonas).

Benign Tumors of the Colon

Most benign tumors of the colon project into the lumen as sessile or pedunculated masses, and hence are called “polyps.” The danger of this designation is that it throws together under one name several types of neoplasm, the potentialities of which differ. The two commonest varieties are the adenomatous polyp and the lipomatous polyp.

General Incidence. Benign tumors of the colon are largely lesions of persons over forty years of age. The sex ratio of adenomas is 3:2 in men, and of lipomas 2:1 in women. The distribution in the parts of the colon is shown in Table 34 (Helwig).

The average number of polyps in any one colon is two. One may be adenomatous and the other lipomatous. Polyps are found in from 5 to 15 per cent of all persons older than forty, the figure varying somewhat with the care used in examination.

Adenomatous Polyps. Pathologic Anatomy. The adenomas may be sessile or pedunculated and vary in size from a millimeter to several centimeters. The stalk is covered by normal mucosa frequently thrown into folds. The bulbous end is irregular and the surface granu-

lar. The stalk is composed of a delicate, vascularized connective tissue. The more peripheral part contains many glands lined by goblet cells, or columnar cells with an acidophilic cytoplasm, or combinations of both. Numerous mitoses may be present. The muscularis mucosa typically extends into the stalk as a continuous or interrupted layer.

Relation to Carcinoma. Microscopic examination of all adenomatous polyps shows that about 10 per cent are malignant, in that there are anaplastic cells and acini and invasion of the stalk. About 30 per cent of all colons with carcinoma also have one or more polyps (Klemperer; Swinton and Warren).

TABLE 34. SITES OF BENIGN TUMORS OF COLON

	Adenomatous Polyps (Per Cent)	Lipomatous Polyps (Per Cent)
Cecum.....	11.8	45
Ascending colon.....	15.4	40
Transverse colon.....	11.8	0
Descending colon.....	8.1	5
Sigmoid.....	27.9	5
Rectum.....	15.8	5
Flexures.....	9.2	0
Total number in 1460 autopsies.....	139	13

The relation of the two conditions is especially well illustrated in hereditary polyposis, in which there are many polyps, and the usual fate is carcinoma beginning in the third or fourth decade of life (Pfeiffer). The inheritance is as a mendelian dominant, not sex-linked.

Causal Factors. The adenomatous polyps are true neoplasms and should not be confused with the “pseudopolyps” formed of redundant and isolated mucosa in the inflammation and ulceration of chronic ulcerative cilitis, for example. The presence of mild inflammation in the polyp may as well be effect as cause.

Other Types of Benign Tumors. The next most frequent benign tumor is the lipoma, usually polypoid, composed of a light-yellow, soft mass of adult fat cells. Rarer types are the leiomyoma (Golden and Stout), fibroma (Hunt), neurofibroma (Glenn), hemangioma (Brown), and carcinoid (Horn), the structures of which are not different from those in other locations.

Clinicopathologic Correlation. As with all tumors of the intestine, ulceration into and obstruction of the lumen are the bases of the clinical signs and symptoms. Most produce no symptoms except for indefinite disturbances, probably related to motility and secretion.

Tumors of the Appendix

The two most common tumors of the appendix are the carcinoid (p. 962) and the adenocarcinoma. The former occurs at least ten times as frequently as the latter. In most



Fig. 328. Polyp of colon. (From the material reported by Dr. Elson Helwig; Surg., Gynec. & Obst., Vol. 76.)

patients symptoms result from acute inflammation secondary to occlusion of the proximal lumen, and a preoperative diagnosis is rarely made (Lesnick and Miller; Ehrlich and Hunter).

Carcinoma of the Colon and Rectum

Carcinoma of the colon and rectum about equally divided between these two parts is, next to that of the stomach, the commonest carcinoma of the alimentary tract.

Pathologic Anatomy. Gross Appearance. Carcinoma of the colon originates either in a preexisting polyp or as a sessile, indurated nodule in the mucosa. With further growth, any one of four types may develop: nodular,

scirrhous, mucinous, and papillary (Stout). The nodular type begins as a round or ovoid ulcer with elevated indurated edges. There follows rapid extension circularly, so that an annular, ulcerated, dark-red mass is formed. The lumen is partially occluded, and the wall is infiltrated. The muscularis is separated by gray tissue, or is entirely destroyed. The peritoneum is thickened, white, opaque, and contracted. The scirrhous type is characterized by excessive growth of firm, fibrous tissue, so that there is a sharp constriction of the gut. The mucinous type is typically a large fungating mass, from which quantities of

ters, and invasion of the vesicle neck. Rarely fistulas form.

Microscopic Appearance. About 90 per cent of all carcinomas of the colon and rectum are adenocarcinomas. Secondary bacterial infection and both acute and chronic inflammation are commonly seen in the stroma and acini.

Grading. Metastases. Most carcinomas of the colon are graded as I or II. Observations indicative of a poor prognosis are: invasion of lymphatics and regional nodes, invasion of veins, absence of mucin in cells, anaplasia of cells, lack of orientation into acini, and

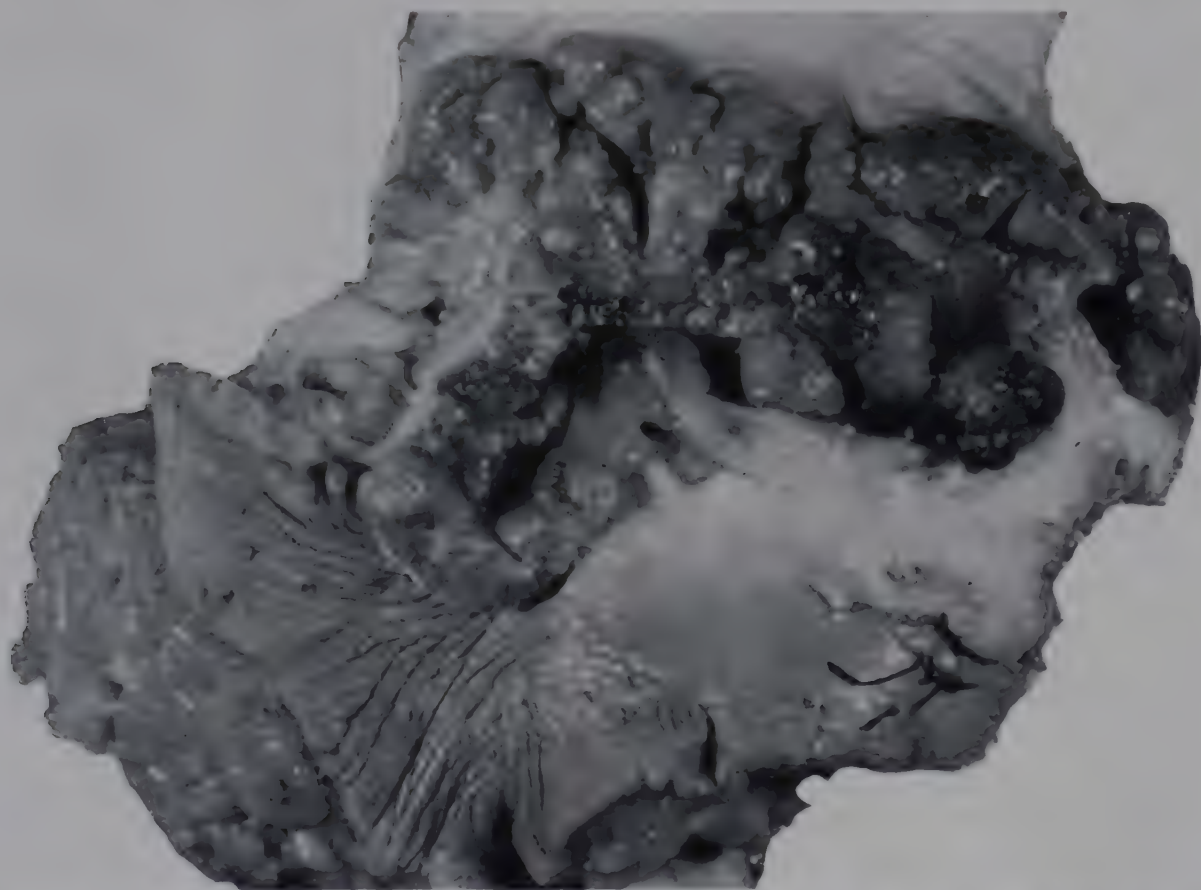


Fig. 329. Carcinoma of rectum extending into anal skin. (Photograph by courtesy of Dr. Lauren Ackerman.)

viscid, clear mucus exude. In the papillary type there are numerous firm papillae with minimal invasion of the wall. In the surrounding mucosa small submucosal or mucosal nodules may be seen. Some regard these as evidence of multicentric origin (Dukes).

Location. About one-half of the carcinomas are in the rectum, one-quarter in the sigmoid, and one-quarter in the remainder of the colon. The rarest sites are hepatic flexure and descending colon.

Secondary Changes and Extension. If there has been obstruction, the lumen orad is dilated and the muscularis hypertrophic. In carcinoma of the rectum and sigmoid, extension anteriorly to the urinary tract is a common late manifestation with obstruction of the ure-

ter. In mucinous carcinoma (Stout). By careful study, metastases to the regional nodes may be observed in as high as 60 per cent (Coller, Kay, and MacIntyre; Kay). Similarly careful study of multiple sections will show vascular invasion in 15 per cent (Grinnell). Distant metastases occur late (Buirge).

Incidence. About 85 per cent of all carcinomas of the colon and rectum are in persons over forty years of age, but the 5 per cent below the age of thirty constitutes a significant percentage of carcinoma in young people. In general, carcinoma of the colon is somewhat more common in women (3:2), and carcinoma of the rectum in men (Buirge).

Causal Factors. There are two definite pre-

cancerous lesions of the colon, polyps and chronic ulcerative colitis. The interrelation of polyps and carcinoma is discussed on page 677. The incidence of carcinoma in ulcerative colitis is low but definite—4 per cent (Bargen, Jackman, and Kerr). In some patients there is a familial incidence (Bargen, Mayo, and Giffin).

Clinicopathologic Correlation. Carcinoma of the colon and rectum produces signs and symptoms by one or more of four mechanisms: (1) irritation, with disturbance in motility—constipation, or diarrhea or alternation, (2) obstruction, (3) ulceration with hemorrhage, (4) irritation of the peritoneum—pain and tenderness.

The difference in the fluidity of the intestinal content is such that it is possible to speak of the clinical syndrome of the right colon and of the left colon. In the cecum and ascending colon the feces are liquid, and a tumor may grow to a large size before producing obstruction or other prominent symptoms. Correspondingly, there is greater opportunity for ulceration and appearance of severe anemia (Alvarez, Judd, MacCarty, and Zimmermann). In the descending colon and sigmoid the feces are dehydrated and formed so that they readily obturate any point where the bowel is even slightly reduced in size. Hence obstruction is an early sign and may come on abruptly (Bockus).

The average survival time without treatment after the diagnosis is established is 10.5 months (Stout). With a palliative colostomy this is increased to 18 months. Of those patients with an operable neoplasm successfully removed, the results are good (Coller and Ransom).

Sarcoma of Colon. The rare sarcomas of the colon are usually lymphosarcomas (Usher and Dixon). Less common are leiomyosarcoma and fibrosarcoma. Malignant melanoma occasionally occurs as a black bulky neoplasm of the rectum.

Cysts and Tumors of the Peritoneum, Mesentery, and Retroperitoneal Tissue

The commonest cyst of the mesentery is a lymphatic cyst resulting from anomalous development or obstruction of the lymphatic vessels. Less frequently seen are cysts derived

from remnants of the wolffian duct and from partial duplication of the intestine, and true dermoid or teratomatous cysts (Lahey and Eckerson).

Primary tumors of the peritoneum are exceedingly rare (Ramsey and Chomet). Solid tumors of the mesentery and retroperitoneal tissues include all types derived from mesenchyme (Hoch). The lipoma is the commonest. Of special interest is the tumor of the retroperitoneal tissue similar in structure to the embryonal nephroma of the kidney.

Epidermoid Carcinoma of the Anus

In contrast with columnar cell carcinoma of the colon, malignant tumors of the anus and anal canal are epidermoid carcinomas. The most frequent site is the anterior wall, and the regional nodes involved are the superior hemorrhoidal group. Most tumors in men are at the anal margin, and in women in the anal canal. The structure shows the usual grades of epidermoid carcinoma. The average age is about sixty years, and about 30 per cent live for five years after treatment (Harvey).

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LXXXIII

Diseases of the Respiratory Tract

The ultimate function of the respiratory tract is to provide an anatomic basis for external respiration. The accomplishment of this function depends on the maintenance of an open airway from the external nares to the terminal alveoli, on the integrity and contractibility of the diaphragm and the muscles of the thoracic wall, and on the normality of the structure of the lung.

Tumors of the Nose and Accessory Nasal Sinuses

Tumors of these structures constitute about 2 per cent of all cases of cancer. They are more common in the nose and nasopharynx than in the sinuses. Within the sinuses the maxillary sinus is most frequently the seat of tumor formation, and the ethmoid, frontal, and sphenoid sinuses follow in that order. The malignant tumors form large, friable masses which project into the nose and invade the surrounding bone, so that the orbit, base of the brain, and skin of the cheek are not infrequently involved. Most of the tumors are of an undifferentiated, anaplastic type of epithelial cell. In many instances a malignant tumor of these structures is found in persons who have for years complained of chronic nasal infection.

Rare tumors of the nose and sinuses are hemangioma, osteoma (Hempstead), chondroma, chordoma, adenoma, ganglioneuroma, melanoma (Smith), and craniopharyngioma (Furstenberg). The chordomas are derived from the remnant of notochordal tissue found in most persons at the base of the skull (Ridpath). The glioma or ganglioneuroma is found as a large, soft mass within the nose and is probably derived from the olfactory bulb (Stout). Tumors derived from the upper teeth may come in contact with or invade the maxillary sinus.

Hypertrophy of the Palatine Tonsil (Adenoids)

Under normal conditions the adenoid grows progressively from birth to about the age of three years. It remains about the same size until puberty when an involutionary process sets in, so that it is again an inconspicuous structure in adults (Todd; Rosenberger). In a number of children the growth is excessive, or the nasal passages are small, so that the palatine tonsil partially or completely occludes the posterior nasopharynx. When removed, it appears as a soft, lobulated structure, covered on one surface by epithelium which dips into the substance of the tonsil to form narrow crypts. These crypts are filled with an inspissated yellow material. Microscopically, the tonsil is seen to be composed of large lymphoid follicles with active germinal centers.

The cause of the overgrowth of this lymphoid tissue in some children is not well understood. The effects of the continued presence of an enlarged palatine tonsil are well known. In addition to obstructing the nasal passages, it may grow laterally and occlude the orifice of the eustachian tube. The crypts of the tonsils also serve as a focus for repeated attacks of upper respiratory infection.

General Effects of Obstruction of the Nose

Longstanding obstruction of the nasal passages brought about by swelling of the mucosa, as in inflammation, by deviations of the nasal septum, by adenoids, or by tumors may produce secondary changes of four types: (1) affecting the ear, (2) affecting the respiratory tract, (3) producing pain, and (4) affecting the lymph nodes.

In children with adenoids, the hypertrophy

and hyperplasia of the adenoid itself, or a similar change in the lymphoid tissue about the mouth of the eustachian tube, may produce occlusion of this structure. Crowe and Baylor found that this occlusion resulted in a loss of hearing for the high tones, and that if the obstruction was removed before the fifteenth year, hearing was restored. The pathologic change in the ear is atrophy of the organ of Corti in the basal 2 mm. of the cochlea (Crowe, Guild, and Polvogt).

The nasal obstruction seen in children with adenoids is undoubtedly the result of the

retention of secretions within the sinuses in consequence of the obstruction of the orifices by swollen mucosa. The pain in tumors results partly from pressure and partly from invasion of nerve sheaths by the tumor.

The lymph nodes about the pharynx and the nodes of the cervical chain drain the superficial structures of the face. In inflammation they are moderately enlarged and tender. Histologically, simple hyperplasia and rarely suppurative inflammation are observed. With malignant tumors, metastases to the lymph nodes depend upon the exact location and

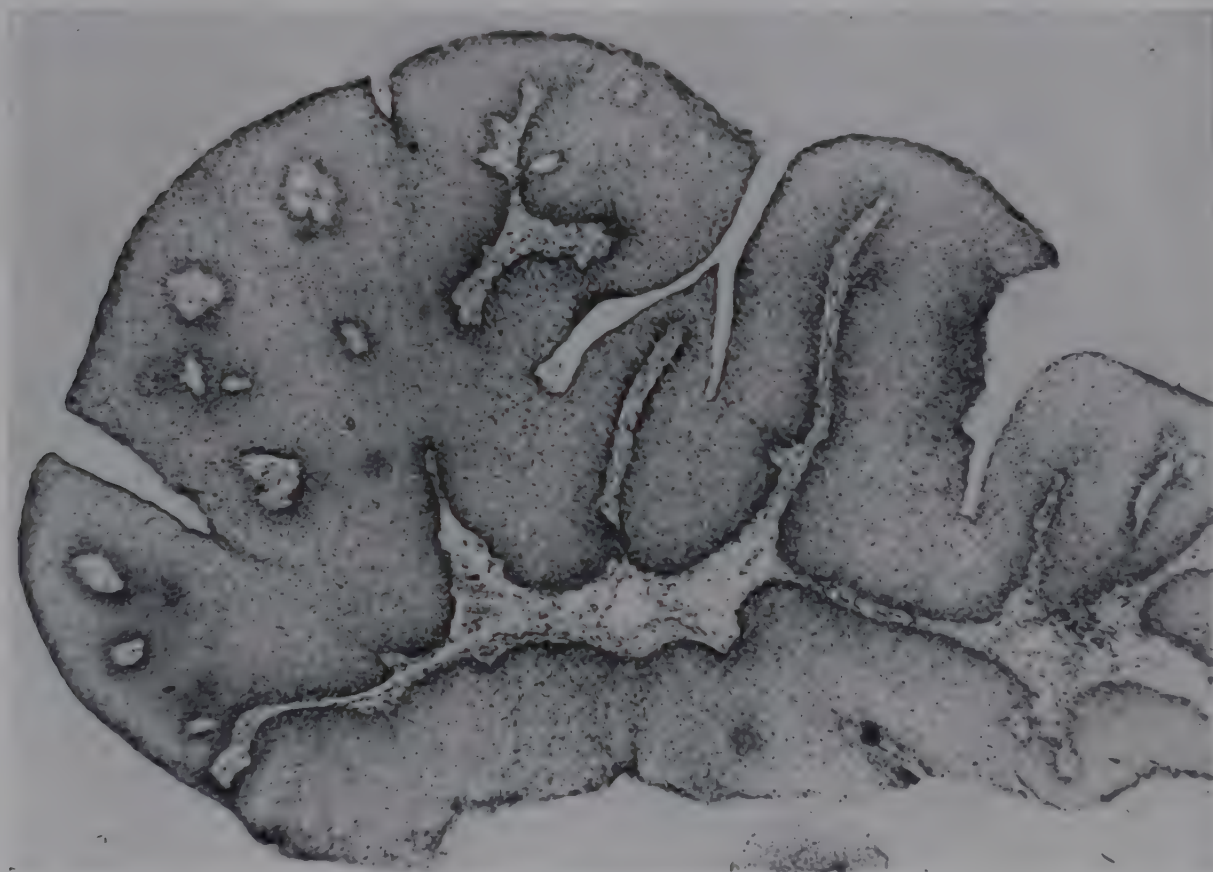


Fig. 330. Papilloma of larynx.

mass of tissue within the superior nasal passages. At about the time the adenoid stops growing (three years), there is a forward drift in the bones of the face, which results in a lowering of the floor of the nose and of the soft palate, and consequent increase in the size of the posterior nasopharynx (Rosenberger). Whether or not a child develops progressive nasal obstruction after this age would appear to depend upon either or both of two factors: enlargement of the adenoids, and failure of this growth of the face. The V-shaped alveolar arch and the Norman arch of the hard palate are frequently observed in children with adenoids, but they are also present in children without adenoids (Brash).

Pain in inflammation of the nose and accessory nasal sinuses is usually caused by the

the type of the tumor. In extrinsic carcinoma of the larynx, metastases to the lymph nodes occur early and are extensive, while in intrinsic carcinoma of the larynx the metastases are late and do not produce large masses. On the other hand lympho-epithelioma of the upper respiratory tract, regardless of its exact point of origin, gives early, bulky metastases.

Papilloma of the Larynx

There are two distinct types of papilloma of the larynx, solitary and multiple. Multiple papillomas are commoner in children; solitary papillomas in adults.

Pathologic Anatomy. Solitary papillomas of the larynx start as small, firm elevations of the mucous membrane of the anterior two-

thirds of the true vocal cords. With continued growth, they may take on a papillary appearance and even ulcerate.

Multiple papillomas of the larynx are commonest in prepuberal children, and appear as small papillary growths, 1 to 5 mm. in height, distributed throughout the larynx as well as on the vocal cords. Microscopically, the papillary growths are observed to be covered by a transitional or stratified squamous epithelium, and the central core to be composed of a loose, moderately well vascularized connective tissue. There may be similar papillomas in the trachea and even in the bronchi (Ferguson and Scott), and aerial metastases to the lungs have been reported (Hitz and Oesterlin). Most of these tumors disappear at puberty. This fact has suggested that the administration of sex hormones might inhibit growth (Broyles; West and Howard).

Clinicopathologic Correlation. Essentially the same symptoms are given by benign tumors of the larynx as by carcinomas. Hoarseness because of the presence of the tumor mass on the true vocal cord is the outstanding symptom in more than 95 per cent of cases. Other symptoms are inconstant. In multiple papillomas obstruction of the larynx or trachea may be a prominent feature and require tracheotomy.

Carcinoma and Other Tumors of the Larynx

It is convenient to divide carcinoma of the larynx into two types: (1) intrinsic, or carcinoma of the vocal cords; and (2) extrinsic, or carcinoma of nearby structures.

Intrinsic Carcinoma of the Larynx. This tumor first appears as a small, firm, elevation of the epithelium of the anterior two-thirds of the vocal cords. With progressive growth it may form a papillary structure or ulceration may supervene. Beneath the epithelium there is slight extension, largely toward the anterior commissure. Most of the tumors are of the epidermoid cell type, although there are occasional undifferentiated cell carcinomas and rare adenocarcinomas.

Extrinsic Carcinoma of the Larynx. The commonest locations for these tumors are the piriform sinus, the aryepiglottic folds, and the epiglottis. In the early stages there are extensive ulceration and destruction of tissue.

Tumors in the piriform sinus are frequently lympho-epitheliomas. Epidermoid carcinoma in this location is less common, and the usual type of extrinsic laryngeal neoplasm is a transitional cell or an undifferentiated cell carcinoma.

Metastases. Metastases are not prominent in intrinsic carcinoma and occur first in the lymph nodes of the deep cervical chain. Met-



Fig. 331. Carcinoma of larynx. (Photograph by courtesy of Dr. Lauren Ackerman.)

astases from tumors of the epiglottis and the surrounding structures first appear in the lymph nodes about the external jugular vein, while tumors from the subglottic regions metastasize to the deep lymph nodes about the larynx, trachea, recurrent laryngeal nerves, and the esophagus.

Incidence. Carcinoma of the larynx constitutes about 3 per cent of all malignant tumors. It is commonest in the sixth decade, and occurs in men nine times as frequently as in women. Despite all forms of treatment the

prognosis is not good; fewer than half of the patients survive five years (Cutler; Welch and Nathanson).

Causal Factors. In many cases of carcinoma of the larynx there is a history of chronic inflammation of this structure, or excessive use of the voice. Not over 1 per cent of persons with carcinoma have had a preceding papilloma. On the basis of study of the vital statistics in England it would appear that the causal factors in carcinoma of the larynx are in general similar to those of carcinoma of the bronchus (p. 694).

Clinicopathologic Correlation. The first symptom of carcinoma of the larynx is usually hoarseness as a result of involvement of the vocal cords. With increase in the size of the tumor there may be gross swelling in the neck, dyspnea, or dysphagia. Either the presence of the tumor mass or ulceration may give rise to sore throat or hemoptysis (Garfin).

Miscellaneous Tumors of the Larynx. Sarcoma of the larynx constitutes about 10 per cent of the malignant tumors of this structure. They are usually of the fibrosarcoma type, but lymphosarcomas and other varieties have been reported. Other tumors of the larynx are rare. There are published reports of mixed tumors of mesenchymal origin such as lipomyxochondroma (New and Erich; Palmer and Mehler), and isolated examples of fibroma, angioma, and mixed tumors of the salivary gland type (Stout). Nodular xanthomatous deposits, either isolated or as a part of general xanthomatosis, have been reported (New). Rarely, amyloid is deposited in nodular form in the submucosa of the larynx and produces a tumorlike nodule with obstruction (New). Inflammatory polyps and nodular masses of tissue resulting from inflammatory processes are not uncommon, and may resemble tumors.

Carcinoma of the Trachea

All tumors of the trachea are rare. About one-third of the reported cases are carcinomas. Fibromas, papillomas, chondromas and osteomas, and sarcomas make up about 10 per cent each.

Pathologic Anatomy. The typical carcinoma of the trachea starts as a small elevated nodule on the superior lateral wall of the lower third of the trachea. It grows slowly and eventually

forms a fungating mass which partially obstructs the lumen of the trachea. About one-half of the tumors are squamous cell carcinomas, and the other half adenocarcinomas. Metastases to the regional nodes occur in about 70 per cent of cases, but metastases to the viscera are uncommon (Culp; Olsen).

Incidence. Carcinoma of the trachea is commonest in late adult life, and is more frequent in men in the ratio of about 6:4.

Causal Factors. No definite causal factors for tumors of the trachea are known. Concrete dust (Weinberg) and trauma have been suggested, but the objective evidence for this postulation is lacking.

Clinicopathologic Correlation. The principal symptoms are the result of the presence of the tumor mass—dyspnea, from obstruction of the lumen of the trachea, and cough, from the invasion of the wall. Rarely, there are difficulty in speaking or hoarseness (from involvement of the recurrent laryngeal nerve) and hemorrhage (from ulceration of the tumor). Late, there may be dysphagia from involvement of the esophagus.

Other Tumors of the Trachea (Jackson and Jackson). Papillomas of the trachea are similar to those in the larynx. Mesenchymal tumors, such as fibroma, chondroma, and osteoma, are probably the same as similar tumors in the bronchi and lungs, and should be designated as "hamartomas." Small masses of bone projecting into the lumen of the trachea are reported in the literature under the name "tracheopathia osteoplastica." Occasionally, a large nodule of thyroidal tissue may project into the lumen of the trachea and appear as a tumor of this structure. Sarcomas of the trachea are rare and are usually of the fibrosarcoma type (Weinberg).

Cysts and Tumors of the Mediastinum

Aside from the metastatic tumors of the mediastinal lymph nodes there are a number of neoplasms which are primary in the mediastinum, notably dermoid cysts, teratomas, tumors derived from the elements of the nervous system, fibromas, and lipomas.

Pathologic Anatomy. Dermoid cysts and teratomas of the mediastinum vary in size from 1 or 2 cm. to 15 to 20 cm. in diameter. They are usually well encapsulated and not adherent to the surrounding tissue. In some

instances, however, there is ulceration into the lungs or bronchi, with secondary infection. The cysts contain hair and sebaceous material, or are occasionally filled with a clear fluid. The cysts are lined with squamous epithelium, and within the fibrous tissue of the wall there are the usual elements of either a dermoid cyst or a teratoma. The commonest elements are sebaceous glands, fat tissue,

bronchi by pressure or ulceration, is present in less than half of the cases. A few of the tumors grow through the thoracic wall to the surface of the body. A tumor arising in the nerve roots or in the sympathetic chain on the posterior thoracic wall may extend into the spinal canal as an hourglass tumor (Heuer). Rarely, cysts of the mediastinum perforate into a bronchus or the trachea.



Fig. 332. Neurofibroma of the superior mediastinum. (Radiograph by courtesy of Dr. Sherwood Moore and Dr. Evarts Graham.)

sweat glands, and cartilage (Rusby; Laipply). Tumors derived from the elements of the nervous system which occur in the chest are ganglioneuroma, neurofibroma, and neuroblastoma. They are sharply encapsulated, and are firm or soft, depending on the amount of connective tissue. On the cut section, especially in the neuroblastoma, foci of necrosis and hemorrhage are seen (Heuer and Andrus). Rarer tumors are lipoma and fibroma (Blades).

Clinicopathologic Correlation. Whether or not a tumor of the mediastinum causes symptoms depends entirely on the size of the tumor and pressure on the intrathoracic viscera. The commonest symptom is a dyspnea on exertion, probably as the result of compression of the pulmonary veins and not from compression of the respiratory tract itself. Pain is usually present and is caused by pressure on the great nerve trunks in the posterior part of the thorax. Cough, from irritation of the

The Lung and Heart in Kyphoscoliosis

In severe grades of kyphosis, scoliosis, and combinations of the two, the deformity of the chest decreases the thoracic volume, and results in atelectasis and fibrosis of the lung. In advanced cases there is also hypertrophy of the right ventricle, and these patients frequently show signs of respiratory embarrassment, and die with pulmonary edema (Kerwin).

Cystic Disease of the Lung

Pathologic Anatomy. Cysts of the lung are of two types: (1) single or multiple, small or large cysts containing air or fluid, and (2) multiple small cysts completely replacing the pulmonary parenchyma—the honeycomb type. The larger cysts are lined with columnar or flattened epithelium, supported on a

submucosa composed of fibrous tissue, elastic fibers, muscle, and cartilage. The cavity is filled with a viscid, cloudy fluid, or with air, or with a mixture of the two. The genesis of the cyst is probably a defect in the growth and canalization of the bronchial anlagen (Ravitch and Hardy).

Clinicopathologic Correlation. Many patients have no signs or symptoms, but the loss of parenchyma occasionally causes recurring attacks of dyspnea and cyanosis in children. The most serious complication is infection of the cyst after it ruptures into a bronchus. On rupture the cloudy fluid is expectorated. Womack and Graham believe that some carcinomas of the bronchi originate in the epithelium of congenital cysts.

Other Congenital Anomalies. Minor anomalies in the formation of the lung are observed frequently: incomplete separation of the lobes by the fissures and additional complete or incomplete fissures forming accessory lobes are common. The azygos lobe, detectable in a radiograph, is located on the posteromedial side of the right upper lobe and is related to an anomalous position of the azygos vein. Rarely, accessory lobes may be separated by a branch of the aorta (Gruenfeld and Gray). Agenesis has been reported (Valle and Graham).

Arteriovenous Fistula of the Lung

Arteriovenous fistulas of the lung are one manifestation of hereditary hemorrhagic telangiectasia. There is a focal mass of dilated arteries and veins with communications between them. The anatomic change tends to cyanosis, clubbing of the hands, slight hypertrophy of the right heart, and polycythemia. A murmur or bruit is usually heard. The inheritance is as a dominant with incomplete penetrance (Goldman).

Atelectasis

Atelectasis is a collapsed or airless state of all or a part of the lung. It may be divided into the type which is found in the newborn infant, discussed in Chapter LXXI, p. 576, and the type which may be found at any later period of life.

Following the neonatal period it is assumed

that the entire lung is fully expanded, and that any collapse after this time represents secondary atelectasis. The appearance of the lung is essentially that described in the newborn infant. The collapsed area is bluish red and firm, and on section the usual architecture of the lung is not discernible.

Pathologic Anatomy. Focal and Massive Collapse. On the basis of the degree of involvement, atelectasis may be divided into "focal" and "massive" collapse of the lung. Focal areas of collapse involving from one to six lobules are a common finding at autopsy, especially in persons in whom the agonal state has lasted for many hours or days. It is commoner in the lower lobes than in the upper lobes, and probably depends upon the obstruction of bronchi by mucus. "Massive collapse" of the lung is a term used to indicate the complete collapse of one lobe or of an entire lung (Coryllos and Birnbaum). It is most frequently observed as a postoperative complication, but may be seen following pneumothorax. Pathologic studies of massive collapse are few, since most of the patients recover, or do not die until secondary changes have occurred. The disease represents simple collapse of the lung as the result of bronchial obstruction. Other factors such as paralysis of the diaphragm, elevation of the diaphragm by distention of the intestines or a tight abdominal dressing, respiratory infection, suppression of the cough reflex voluntarily or by drugs, and the general lack of muscular tone, undoubtedly play a role (Moore). At the rare autopsy the alveoli are seen to be filled with a serosanguineous fluid, or pneumonia is observed, involving the greater part of a lobe or lung (Kaunitz). These types of atelectasis may be termed "obstructive atelectasis."

Compression or Nonobstructive Atelectasis. The same pathologic picture is observed in accumulations of air and fluid in the pleural cavity, and this type may be designated "compression" or "nonobstructive atelectasis." In the obstructive types the air trapped beyond the obstruction is absorbed by the blood stream (Coryllos and Birnbaum), while in the nonobstructive types the air is pressed from the lung by the air or fluid under pressure in the pleural cavity. Air may be introduced artificially into the pleural cavity as in the treatment of pulmonary tuberculosis by

pneumothorax, or it may be derived from the rupture of an emphysematous bleb or bulla. In either type of atelectasis, if the collapse persists for several weeks or months, there is fibrous thickening of the pleura and fibrosis of the lung substance, which offers a resistance to reexpansion (Wolfe, Wang, and Van Allen). The lymphatic vessels of the lung dilate, and there is probably inadequate drainage (Hilton).

Relation of Atelectasis to Pneumonia. The complete obstruction of a bronchus leads to

Emphysema. Mediastinal and Subcutaneous Emphysema. Pneumothorax

Emphysema was originally described by Laënnec as an overdistention of the lungs and an enlargement and coalescence of the pulmonary alveoli. Since that time, however, the term has been applied to many different conditions. In order to clarify this situation we may divide the condition into four types: (1) true pulmonary emphysema, the original

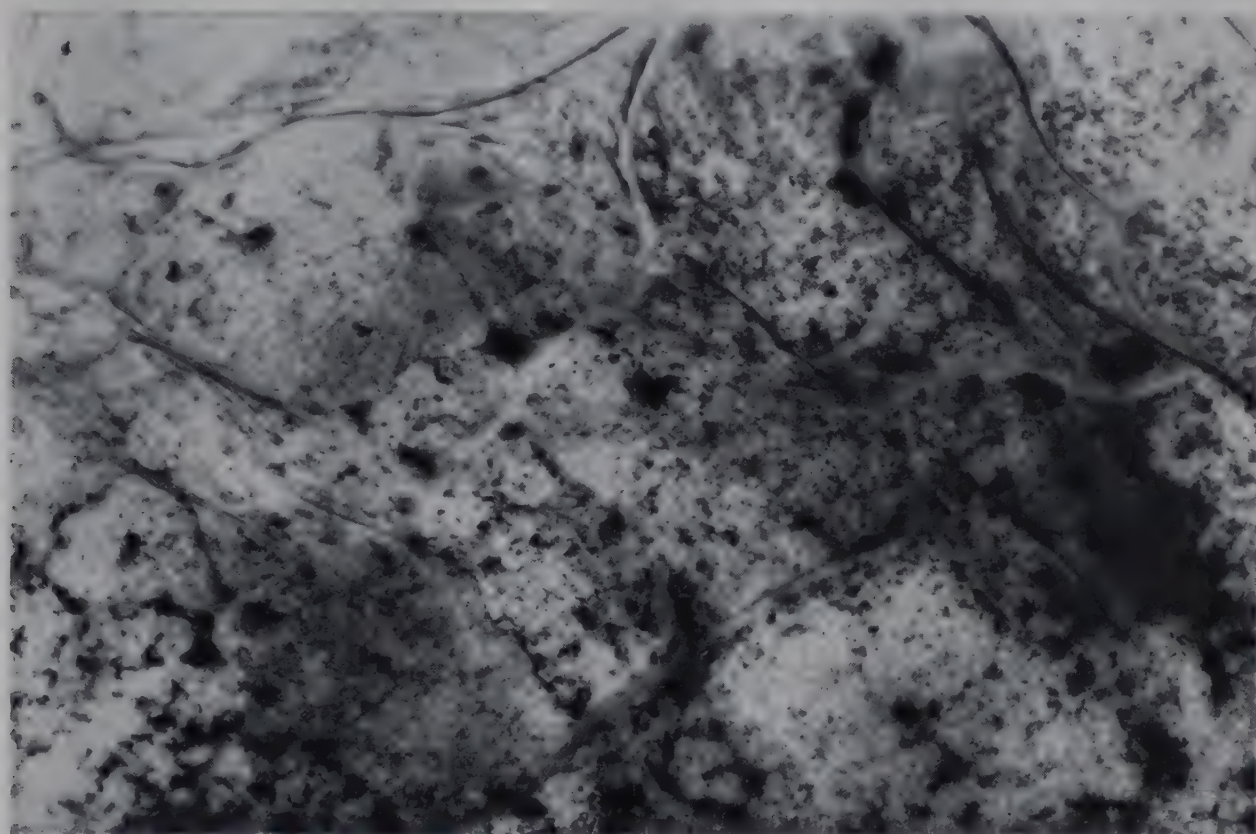


Fig. 333. Surface of lung in emphysema. Note the small vesicles representing confluent alveoli.

the accumulation of secretions containing bacteria within the area of a lung deprived of drainage, and it is generally believed that the onset of bronchopneumonia may depend on a preceding atelectasis.

Physiologic Changes with Atelectasis and Clinicopathologic Correlation. In focal atelectasis there are probably no physiologic changes and no signs or symptoms except an area of dullness upon percussion of the chest. In massive atelectasis there are definite alterations in the physiologic action of both the lungs and heart. There is a decrease of blood flow through the lung (Fine and Drinker) and a decreased vital capacity, decreased residual air, and an increase of the alveolar and blood carbon dioxide (Richards, Riley, and Hiscock). In many cases these changes in the function of the heart and lungs lead to dyspnea and cyanosis.

concept of Laënnec, in which the air sacs of the lung are visible to the naked eye and represent the coalescence of a group of pre-existing smaller air sacs; (2) overdistention of the lungs, in which the alveoli are large and visible to the naked eye, but are not coalesced; (3) interstitial emphysema, in which there is an accumulation of air in the interstitial tissue of the lung, mediastinum, or subcutaneous tissue; and (4) the accumulation of air in the pleural cavity, termed "pneumothorax." The close relation of all of these conditions has led to the confusion.

Pulmonary Emphysema. In true pulmonary emphysema the thoracic cage is enlarged, particularly in the anteroposterior diameter. Upon removal of the sternum one of two conditions may be found: either the lungs completely fill the pleural cavity and bulge through the incision, or the lungs are collapsed and occupy

not over half of the pleural cavity. These may be designated "obstructive emphysema" and "nonobstructive" or "senile emphysema," respectively. In both instances, the air spaces of the lung are clearly visible to the naked eye. Microscopically, smaller or larger spaces are observed to be formed by the coalescence of alveoli. Into these spaces project short segments of alveolar walls, with knoblike thickenings on the ends, termed "spurs." The alveolar walls which remain contain an increased amount of fibrous tissue and relatively few

sicians who play wind instruments, as Laënnec suggested, any oftener than in the general population (Jagic and Lipiner).

Nonobstructive Emphysema. This type, or "small-lung" emphysema, is found with increasing frequency with increasing age, and is generally believed to be one of the involutionary processes of senility. A loss of the elastic fibrillae in the alveolar septa, usual in old age, could satisfactorily explain the development of emphysema, although it would not explain the anteroposterior enlargement of

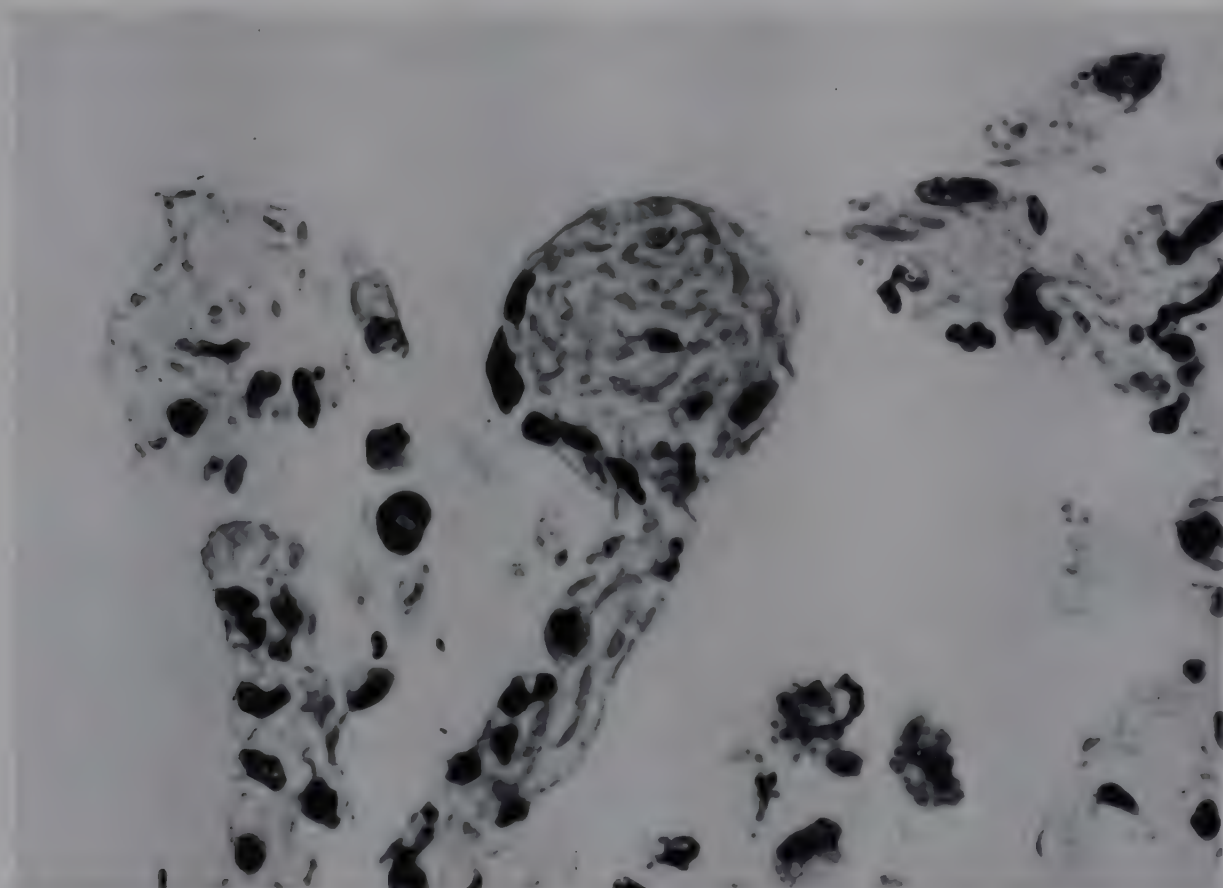


Fig. 334. Fibrous ball on end of a ruptured alveolar wall in emphysema.

capillary blood vessels. There is also a decrease in the amount of elastic tissue. It is generally assumed that this appearance is the result of rupture of alveolar walls. Hartroft has given evidence that the basic change is not rupture but overdistention. The small arterioles are thickened, and the larger branches of the pulmonary artery show slight to moderate arteriosclerosis.

Obstructive Emphysema. In this condition the lung is large. Many have designated it "large-lung" emphysema. It is an almost constant finding in asthma, where there is stenosis of the medium-sized and smaller bronchi (MacDonald). It is occasionally found in association with stenosis of a bronchus by a tuberculous lymph node (Spivek). Emphysema does not occur in glass-blowers and mu-

the thoracic cage. Kountz and Alexander have suggested that osteoporosis of the vertebrae results in a straightening of the normal dorsal kyphosis, which in turn elevates and separates the ribs and results in enlargement of the chest. Others have suggested that calcification of the costal cartilages is a factor.

Focal Emphysema. About tuberculous scars of the apex (Korol) and other focal areas of fibrosis in the lung, and in association with pneumoconiosis (Cummins), there is the typical picture of true pulmonary emphysema in small or large foci. The air spaces are large, with many spurs extending into them. It would appear that this lesion is the result of both a destruction of pulmonary tissue and the contraction of scar tissue.

Overdistention of the Lungs. In many cases

of acute obstruction of the respiratory tract, particularly in instances of fatal hemoptysis, where many bronchi are partially obstructed by blood, the vigorous efforts at respiration trap air within the alveoli and overdistend them. There is thinning of the alveolar walls, but no loss of pulmonary tissue, so that the condition is not the same as true pulmonary emphysema.

Complemental Emphysema and Overdistention of the Lungs. In conditions which cause either destruction or atelectasis of a por-

cent of cases of emphysema and at autopsy in about 50 per cent. There are no definitive observations to associate the presence or degree of hypertrophy of the right ventricle with the severity or duration of the emphysema (Kountz, Alexander, and Prinzmetal).

There is an increase of intrapleural pressure and of the peripheral venous pressure (Kountz, Pearson, and Koenig). There are an increase of the residual air and a reduction in vital capacity (Hurtado, Fray, and McCann). These alterations in the function



Fig. 335. Pneumothorax on the left side. (Radiograph by courtesy of Dr. Sherwood Moore.)

tion of the lung, the remaining part may present an emphysematous appearance. In acute conditions such as lobar pneumonia or compression atelectasis from pleural effusion, this is really an overdistention of the lung. In chronic conditions such as tuberculosis and pneumoconiosis it is a true pulmonary emphysema. The usual term "compensatory emphysema" is inappropriate because emphysema is a pathologic process which leads to an inability of the lung to accomplish its given function. No process of this nature can be compensatory.

Secondary Changes and Clinicopathologic Correlation. Hypertrophy of the right ventricle is observed clinically in about 25 per

cent of cases of emphysema and at autopsy in about 50 per cent. There are no definitive observations to associate the presence or degree of hypertrophy of the right ventricle with the severity or duration of the emphysema (Kountz, Alexander, and Prinzmetal). There is an increase of intrapleural pressure and of the peripheral venous pressure (Kountz, Pearson, and Koenig). There are an increase of the residual air and a reduction in vital capacity (Hurtado, Fray, and McCann). These alterations in the function of the lung eventually lead in many patients to death, with the general appearance of cardiac failure. The clinical symptoms, however, are the manifestations of pulmonary failure (Miller and Rappaport; Kountz, Alexander, and Dowell). The gradual destruction of alveolar walls leads to a diminution of the ability of the lung to serve its function in external respiration. If it also loses the other function of eliminating fluid and washing the surface of the lung, the fluid accumulates in the alveoli as acute pulmonary edema.

Interstitial Emphysema. By this term is meant the accumulation of air in tissue spaces. In the lung it appears as small blebs in the pleura (Miller), in the interlobular

septa, and in the loose connective tissue about the great vessels and bronchi. The blebs can be pushed from place to place by gentle pressure. The lesion is seen following too vigorous attempts at artificial respiration in newborn infants (Marcotte, Philips, Adams, and Livingstone). In adults it is usually found in association with a preexisting disease of the lung, such as acute inflammations (Neffson and Bullowa) or chronic inflammations with fibrosis. It is occasionally observed in an apparently normal lung (Hamman). Numerous pathologic studies show that the source of the air in interstitial emphysema is the rupture of small respiratory bronchioles. The act of respiration draws air out into the tissues, and it dissects along the loose tissue of the septa and about the vessels, and thus reaches the pleura or the hilum of the lung. In some instances the accumulation about the great vessels may be sufficient to cause partial compression of them (Macklin). The rupture of a subpleural bleb may initiate pneumothorax. From the hilum of the lung the air may dissect into the mediastinum and appear in the subcutaneous tissues of the neck. In exceptional instances interstitial emphysema of the lung may spread directly to the subcutaneous tissues of the thorax through pleural adhesions (Dolgopol and Stern). If, at the time interstitial emphysema develops, there is infection of the bronchi or lungs, this infection may follow the course of the air and result in acute mediastinitis or inflammation of the subcutaneous tissues of the neck and thorax (Macklin).

Pneumothorax. As the result of trauma to the thoracic wall, or simple rupture of a bleb (Kirschner) or a bulla (Willcox) on the surface of the lung, it may accumulate in the pleural cavity under atmospheric pressure. Under other circumstances air may be admitted to the pleural cavity through a rupture of alveoli or of a bronchus, but cannot be pushed out through the same opening during expiration, and there sometimes results then what is called a "tension pneumothorax." In either condition the lung is collapsed and shows a typical picture of atelectasis. Those parts of the lung held to the thoracic wall by adhesions cannot of course collapse. Pneumothorax may follow perforation of a bronchus or occur after tracheotomy (Michaels). Rarerly, pneumothorax is bilateral (Werner and Thearle).

Acute Diffuse Interstitial Fibrosis of Lungs

An acute progressive disease producing dyspnea and cyanosis was first described by Hammon and Rich. The anatomic features are an exudate in the alveoli of fluid, red cells, and a few leukocytes, a cuboidal cell lining the alveoli, necrosis of alveolar and bronchiolar epithelium, hyaline membranes in the alveoli, edema and fibrin deposit in the alveolar walls, diffuse interstitial fibrosis and organization of the alveolar exudate, and infiltration of eosinophils in the fibrous tissue. The cause is unknown. Bacteria are not present in the tissues.

Bronchiectasis

Pathologic Anatomy. Bronchiectasis is a permanent dilatation of one or more bronchi. The lumens of the bronchi are increased in diameter from two to five times, and the mucosa is swollen, soft, and redundant. The walls of the bronchi are thick and firm. The lumens contain a thick, yellow, tenacious secretion. The surrounding pulmonary tissue shows a variety of changes, dependent upon the severity and stage of the disease, from simple atelectasis to extensive organizing pneumonia with abscess formation. Terms such as "fusiform," "saccular," or "cylindrical" are applied to describe the exact shape of the dilated bronchi (Ogilvie).

The epithelium may retain the usual ciliated, columnar appearance, but more often there is a pseudostratification of the epithelium with loss of cilia. In foci there may be ulceration or metaplasia of the epithelium to a stratified squamous type. Overlying the epithelium there is a mucinous secretion in which numerous polymorphonuclear leukocytes and lymphocytes are embedded. In the submucosa there is an extensive loss of elastic fibrillae and of the smooth muscle fibers. The submucosa is thickened by loose granulation tissue, infiltrated with large numbers of lymphocytes and a few polymorphonuclear leukocytes. In severe cases the cartilage of the bronchial wall is eroded and replaced by fibrous tissue. The small arterioles in the wall of the bronchus are thickened by a proliferation of the intima (Robinson; Erb). In some cases a localized area is expanded into a

cavity, and complete loss of the entire bronchial wall may be seen microscopically. This is a bronchiectatic abscess, and should be distinguished from a saccular bronchiectasis, in which at least a part of the wall of the bronchus is retained.

Atrophic Bronchiectasis. In an occasional case the picture is different. The lumens of the bronchi are dilated, but the walls are thinner than normal. The elastic fibrillae and

right lower lobe (Perry and King). The clinical disease may be observed at any age, but the history in most cases dates the onset of the illness to some disease during childhood, such as pneumonia or whooping cough.

The pathogenesis of bronchiectasis is a difficult question (Miller). In general three factors must be considered: (1) developmental factors, (2) disturbance of bronchial function, and (3) the role of infection.



Fig. 336. Bronchiectasis.

muscle are present in normal amount and in normal arrangement. There is no evidence of active inflammation. This lesion may be considered another variety of bronchiectasis, namely atrophic.

Bacterial Causes. Bacteriologic examination of either the secretions or the tissue of the lung in bronchiectasis reveals any of a wide variety of organisms. The hemolytic streptococcus, the staphylococcus, and fusiform bacilli are the commonest (Greely).

Causal Factors and Pathogenesis. Bronchiectasis is commoner in the lower lobes than in the upper lobes, and in the left than in the

Developmental Factors. The frequency of onset of the disease in childhood suggests that some congenital anomaly of the lung or bronchial tree forms the basis of the pathologic change. Recent studies of the growth of the lung during childhood lend some support to this theory (Strukow). The lung continues to grow until about the twelfth year, and a severe infection of the bronchi during this period might conceivably result in a disturbance of the subsequent growth of the bronchi. There is apparently a close association between bronchiectasis and congenital cystic disease of the lung, but the two are dis-

tinct entities, and there is no evidence that cystic disease plays any role in the pathogenesis of bronchiectasis.

Disturbance of Bronchial Function. The second factor is largely concerned with the inability of the bronchial tree to remove secretions, and with the effect of the increased pressure brought about during a cough. Unless one assumes that there is a congenital defect in the function of the bronchial tree, the failure to remove bronchial secretions cannot be a causal agent, since it does not appear until the disease is well developed. Increased pressure, because of coughing, in the bronchial tree of an expanded lung will be imme-

result in a weakening of the wall. There is also the possibility that these diseases may cause sufficient ulceration and excavation of tissue to bring about an increase in the size of the bronchi. Many cases of bronchiectasis have associated sinusitis, which is probably a complication and not a cause (Goodale).

The high incidence of bronchiectasis in patients with dextrocardia and situs inversus is unexplained (Olsen).

Carcinoma of the Bronchus

Pathologic Anatomy. Carcinoma of the bronchus, in about 90 per cent of instances,



Fig. 337. Carcinoma of bronchus. (Photograph by courtesy of Dr. Lauren Ackerman.)

diately transmitted to the alveoli surrounding the bronchi. There can be no more dilatation of the bronchi than of the alveoli, since they are pressing against one another. On the other hand, if the surrounding pulmonary tissue is collapsed, an increase of pressure within the bronchi could result in dilatation. It would therefore appear that atelectasis plays an important part in the pathogenesis of bronchiectasis—possibly the most important part (Andrus).

Infection. The role of infection is also difficult to evaluate, since in all clinical cases of bronchiectasis there is an infection, and this infection may be either the cause or effect. On the other hand, there is logic in the belief that diseases such as influenza (Opie, Blake, Small, and Rivers) and severe bronchitis (McNeil, Macgregor, and Alexander), which cause ulceration and destruction of the mucosa and submucosa of the bronchi,

appears grossly as a firm, grayish white mass at the hilum of the lung, surrounding one or more of the major bronchi. The walls of the bronchi are thickened by infiltration with grayish white tissue, in which there are numerous small yellow flecks. In one bronchus the mucosa is usually destroyed and replaced by a soft ulcerating mass which obstructs the lumen. In the adjacent mucous membrane of this bronchus and of the contiguous bronchi, there may be small nodules, 1 to 2 mm. in diameter, representing mucous membrane metastases. If the stenosis of one or more bronchi is advanced, the pyramid of pulmonary tissue supplied by this bronchus is firm, and on section little of the architecture of the lung is seen. In its place there are irregular confluent areas of gray fibrillar tissue, containing foci of small, bright yellow flecks. Although microscopically a moderate number of tumor cells may be seen in this area

of lung, the important pathologic change is an organizing pneumonia dependent on the bronchial stenosis.

Peripheral Tumor of Lung. In less than 10 per cent of all cases of carcinoma of the bronchus there is a solitary nodule in the

the distribution of metastases in the first three of the types (Table 35).

Squamous cell carcinoma is commonest in the eparterial and hyparterial branches of the bronchi. The cells are polygonal, show intercellular bridges, and are frequently ar-

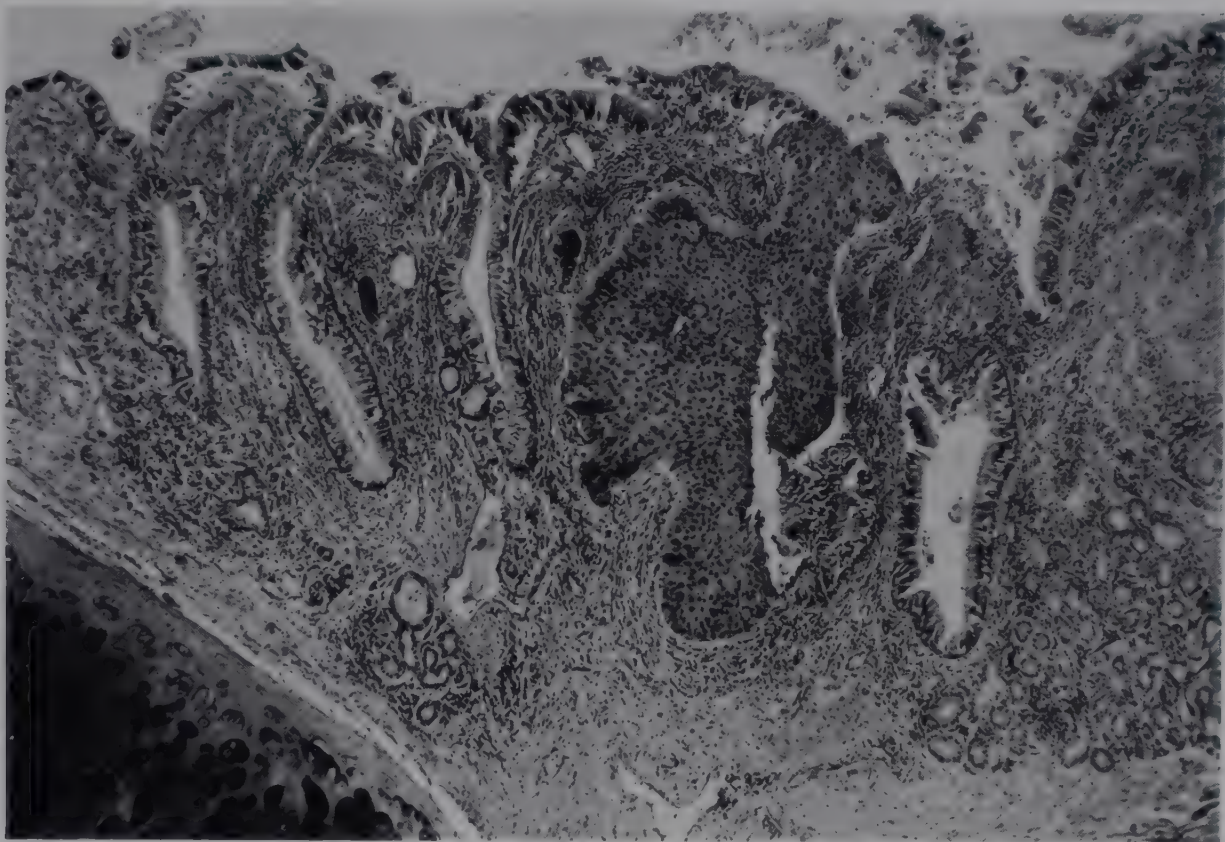


Fig. 338. Squamous cell carcinoma of a bronchus.

periphery of the lung, which varies from 3 to 7 cm. in diameter. This type is designated as the “peripheral tumor of the lung.” The pleura is thickened over the nodule, and frequently there is central umbilication or a fibrous scar.

ranged in whorls, some of which are keratinized to form the characteristic epithelial pearl (Fig. 338). Adenocarcinoma occurs most frequently in the secondary and tertiary bronchi. The cells are cuboidal or low colum-

TABLE 35. METASTASES IN CARCINOMA OF BRONCHUS

Metastases To:	Per Cent with Metastases		
	Small Cell Carcinoma	Squamous Cell Carcinoma	Adenocarcinoma
Cervical lymph nodes.....	48	0	27
Liver.....	48	12	27
Adrenals.....	54	12	64
Other lung.....	11	12	55
Spleen.....	17	0	23
Brain.....	33	53	36

Classification. Most carcinomas of the bronchus can be classified into four types: squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and undifferentiated cell carcinoma. The usefulness of this classification may be seen from the studies of Koletsky on

nar, and are arranged for the most part in an acinic form. The individual tumor cells of the small cell carcinoma, frequently designated “oat-cell carcinoma,” may be either round or spindle-shaped, and are collected into small or large masses. These masses are completely

devoid of reticulin fibers, thus establishing this tumor as a carcinoma and not a sarcoma. The small cell carcinoma is most frequently found in the main stem bronchi to the right or left lung, and characteristically the tracheobronchial lymph nodes are enlarged. This enlargement of the lymph nodes and the inconspicuousness of the tumor in the bronchus led many early pathologists to regard this type of tumor as a lymphosarcoma of the mediastinal lymph nodes. In view of the sharp differences in the location of the tumors, and in the percentage of metastases in the various tumor types outlined (Table 35), the usual form of grading on the basis of anaplasia seems unnecessary (Tuttle and Womack).

Histogenesis. Most carcinomas of the bronchi which are observed at autopsy are so large that it is impossible to demonstrate the exact point of origin. In examples which have been incidentally encountered in routine sections, the cell of origin has been the epithelium of the bronchi (Karsner and Saphir). There is little evidence that the tumor which is frequently designated as "carcinoma of the lung" is ever derived from the alveolar epithelium (Neubuerger and Geever). Rarely, two or more primary tumors of the bronchi can be demonstrated (Lindberg). Womack and Graham concluded that most tumors of the lung and bronchi (except epidermoid carcinomas) really represent a single tumor type, a mixed tumor of epithelial and mesenchymal elements. They consider that they are derived from fetal rests of bronchial buds and that all variations and transitions from a benign to a malignant tumor can be observed.

In from 85 to 90 per cent of the cases as observed at autopsy there are metastases to the tracheobronchial lymph nodes. Systemic metastases have been discussed. The high incidence of metastases to the brain and to the adrenal glands as compared to other primary carcinomas deserves emphasis (King and Ford).

Incidence. Carcinoma of the bronchus is about eight times as common in men as in women, and reaches the highest incidence during the sixth and seventh decades (Weller). Carefully compiled autopsy figures for the last forty years clearly indicate that more cases of carcinoma of the bronchus are seen at the present time than at the beginning of the century (Macklin). Greater longevity and

increased exactness of diagnosis have been suggested as factors in this apparent increased incidence. Statistical studies, however, show that neither of these causes can entirely account for it (Rosahn). One must assume that there is some causal agent more prevalent today than in former times.

The distribution in the various lobes of the lung on the basis of 784 cases collected from the literature (Fischer) is as follows:

Right upper lobe.....	148
Left upper lobe.....	130
Right lower lobe.....	129
Left lower lobe.....	105
Right middle lobe.....	15

Causal Factors. Occupation. Approximately 50 per cent of the deaths in the workmen in the cobalt mines of Schneeberg and Joachimsthal are caused by carcinoma of the bronchus, an incidence which is not found in any other locality or in any other occupation throughout the world. The tumors in these men are similar in all respects to those found in other persons. The ore in the mines is rich in cobalt, but also contains at least two substances which are known to be carcinogenic: pitchblende, which is radioactive, and arsenic. Careful studies indicate that the radioactivity is probably the responsible agent (Schmorl; Pirchan and Šikl).

There is some evidence in England that carcinoma of the bronchus is commoner in road workers and in those in sustained contact with coal-tar products and tobacco than in the general population. There is, however, no evidence that carcinoma of the bronchus occurs more frequently in chauffeurs and truck drivers than in other people (Kennaway and Kennaway). These results would indicate that tar on the roads may be an important factor, but that the use of internal combustion engines is not an important factor in the greater incidence of this disease at the present time than forty years ago.

Tobacco. The greater use of tobacco by both men and women in the last twenty years has led some to postulate that this substance is a cause of carcinoma of the bronchus (Müller). Wynder and Graham have collected statistical evidence that a history of moderate or excessive smoking is the rule in patients with carcinoma of the lung.

Influenza and Other Infections. Following the influenza epidemic of 1917-1919 path-

ologists noted hyperplasia and metaplasia of the bronchial epithelium in many patients, and some went so far as to predict an increase in the incidence of carcinoma of the bronchus during the succeeding ten or twenty years (Winternitz). Statistical studies show, however, that the increase in carcinoma of the bronchus started some five to ten years before the pandemic of influenza in 1917. Likewise, there was no increase of carcinoma of the bronchus following the pandemic of influenza in 1896.

Syphilis and Tuberculosis. Except for rare instances, no definite relation between carcinoma of the bronchus and tuberculosis (Basch) or syphilis can be established.

Pneumoconiosis. There is no evidence that anthracosis has any influence on the incidence of carcinoma of the bronchus. On the other hand there is both positive and negative evidence that silicosis may play some part. On the negative side, the careful studies of the Miners' Phthisis Medical Bureau of South Africa in 1935 compared the incidence of carcinoma of the bronchus in European miners having silicosis, in European miners without silicosis, and in European men who had never been underground. The incidence in the autopsies of these three groups was 0.70 per cent, 0.71 per cent, and 0.93 per cent respectively, with approximately 1500 autopsies in each group. On the positive side, the reports from the University of Toronto show an incidence of 8 per cent of carcinoma of the bronchus in cases of silicosis, as compared with 1.17 per cent in 4500 unselected autopsies (Klotz). Although the Schneeberg miners show a considerable degree of pneumoconiosis, pathologic studies have not demonstrated a relation between anthracochalciosis and the frequent carcinomas in these persons. The only available studies concerning asbestosis indicate a higher incidence of carcinoma of the bronchus in association with it, approaching 20 per cent (Homburger).

Other Factors. In isolated cases it is possible that direct trauma to the thorax is a causal factor in carcinoma of the bronchus (Wells and Cannon). In a few examples of the disease a family history of malignant tumors may be secured (Weller).

Clinicopathologic Correlation. The commonest symptoms of carcinoma of the bronchus are cough, pain, dyspnea, pyrexia, and

hemoptysis. The cough is probably the result of the presence of the tumor in the wall of the bronchus, or pressure upon the wall of the bronchus. At times, especially in the latter instance, the cough is paroxysmal. Pain is caused by invasion of the pleura, or pressure of the primary or secondary nodules of the tumor on the intercostal nerves or on the nerve roots about the vertebral column. Rarely, the pain is caused by pleurisy. Hemoptysis indicates some ulceration into a bronchus and is usually not extensive. The expectoration and pyrexia are in general the result of a secondary infection of the pulmonary tissue, distal to the point of bronchial stenosis. Infrequently, the tumor may invade the pericardium, surround the great vessels, and produce edema of the head and neck (Simpson). The average survival time after diagnosis is slightly over a year (Tuttle and Womack). Greater use of histologic methods for the demonstration of tumor cells in the sputum (Barrett) and in pleural fluids (Foot) has increased the accuracy of diagnosis.

Alveolar Cell Tumors of the Lung

In contrast with the usual carcinoma of the lung which is primary in a bronchus, there is a tumor which apparently originates from the alveolar epithelium (Laipply and Fisher; Swan).

The tumor may appear grossly as multiple gray-yellow soft nodules throughout both lungs or as a diffuse gray infiltration of the lungs. The cellular type is the same in both, a columnar cell with nasal nucleus and an eosinophilic cytoplasm. Rarely there are cilia, and in some the cells form mucin. The cells line the preexisting alveoli.

Some tumors are benign—pulmonary adenomatosis—while others show anaplasia, invasion, and metastases—alveolar cell carcinoma.

A similar lesion to the benign type is observed in the lungs of sheep, mice, horses, and guinea pigs. In sheep and horses it is called jagziekte disease. There is some evidence the animal disease is caused by a virus.

Miscellaneous Tumors of the Bronchi and Lungs

Adenoma. Adenomas usually occur in the larger bronchi near the hilum, and are sessile

or pedunculated masses which project into the lumen and obstruct it. The tumor is usually covered by the bronchial mucosa, which rarely shows ulceration, but not infrequently there is metaplasia of the epithelium. Microscopically, the typical adenoma is seen to be composed of solid or glandular nests of polygonal or cuboidal epithelial cells, embedded in a loose, richly vascularized connective tissue. Grossly, the tumors appear circumscribed and may appear encapsulated, but microscopically there is distinct invasion of variable degree into the surrounding parenchyma and at times

are found beneath the pleura, or less frequently projecting into the lumen of a bronchus. These tumors are firm, and are composed of lobules of grayish white, opaque, or translucent cartilage. The lobules are separated from one another by narrow connective tissue trabeculae. Occasionally, adipose tissue is grossly discernible. Microscopically, the tumors are seen to be composed of islands of hyalin or fibro-elastic cartilage, interspersed in a connective tissue background. Within the connective tissue there is a variable amount of adipose tissue. Rarely, there are smooth

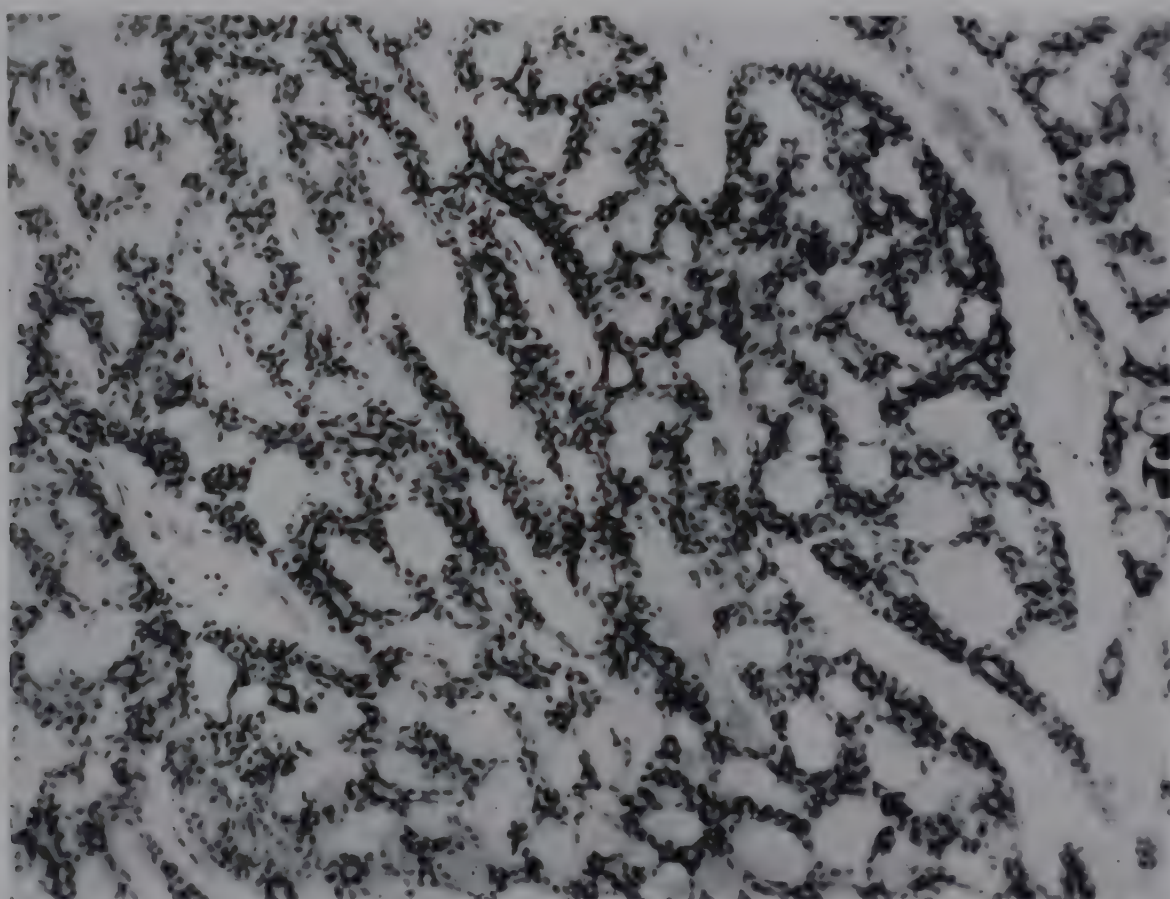


Fig. 339. Adenoma of bronchus. (Case reported by Anderson: J. Thoracic Surg., Vol. 12.)

permeation of the lymphatics (Womack and Graham). Mitotic figures are rare. In the glandular acini there may be a small amount of mucus (Stout).

Adenomas occur as frequently or perhaps more frequently in women than in men (Kramer and Son). They occur at any age, and over 60 per cent of the patients are less than thirty-five years (Reisner). The difference in the sex ratio and in the age incidence of the adenoma and carcinoma is strong evidence of an essential difference in the two tumors. Rarely, a histologically typical adenoma metastasizes, and a transition between adenoma and carcinoma is observable (Anderson).

Hamartoma. Rarely, at autopsy, small tumor nodules not exceeding 1 cm. in diameter

muscle fibers. Irregularly deformed spaces lined by cuboidal or columnar epithelium are common (Hickey and Simpson).

Hemangiomas are frequently associated with polycythemia, and a loud bruit may be heard (Hepburn and Dauphinee).

Tumors of the Pulmonary Apex

Pancoast in 1924 first called attention to the association of a tumor mass at the apex of the chest and a definite clinical syndrome composed of unilateral pain in the shoulder girdle, Horner's syndrome (homolateral ptosis of the upper eyelid, myosis, enophthalmos, and anhydrosis and flushing of the face), and paresis of the hand. An abnormal shadow in the apex of the lung and erosion of the adja-

cent ribs and vertebrae may be seen in radiographs. Pancoast proposed the name "superior pulmonary sulcus tumor."

In the majority of cases this symptom-complex is caused by a primary carcinoma in the apex of lung which has extended through the parietal pleura and into the surrounding structures of the neck. The tumors are epidermoid

Horner's syndrome is the result of destruction of the thoracocervical sympathetic chain at or above the first thoracic sympathetic ganglion (Ray). Rarely, the tumor may invade the phrenic and laryngeal nerves or grow into the vertebral canal through the intervertebral foramina to form an hourglass mass with compression of the cord.



Fig. 340. Diagram of an anatomical preparation showing region invaded by a tumor at the left thoracic apex. The clavicle and sections of the subclavian artery and vein have been removed. The apex of the lung together with parietal pleura is depressed with a retractor. The cervical nerves to the brachial plexus (fifth, sixth, seventh, and eighth cervicals) are seen emerging from their intervertebral foramina. The first and second thoracic nerves are also seen. The exposed sympathetic chain, from below upward, shows the second thoracic ganglion, the first thoracic ganglion, the inferior cervical ganglion, and the midcervical ganglion with their respective rami. (Ray, Surg., Gynec. & Obst., Vol. 67.)

carcinomas or adenocarcinomas derived from apical bronchi or branchial clefts. Rare examples of an intrathoracic sympathoblastoma (Frost and Wolpaw), neurogenic fibrosarcoma (Ray), thymic carcinoma (Browder and DeVeer), and metastases from carcinoma of the esophagus (Ray), stomach (Tobias), breast (Evans), and pancreas (Ray) have been reported.

The pain, paresis, and sensory disturbances in the shoulder girdle and upper extremity probably results in the early stages from impingement of the tumor on the parietal pleura, and later from invasion of the brachial plexus or the nerve roots of the upper thoracic segments as they emerge from the foramina.

Mesothelioma of the Pleura

In a few cases at autopsy the visceral pleura is thickened to 1 or 2 cm., and is composed of a dense white tissue in which there are a few yellow flecks. The parietal pleura may be involved in a similar manner, but usually to a lesser degree. The thickened pleura is made up of broad, interlacing bands of connective tissue with isolated groups of polygonal or round cells. These cells are irregular in size and shape, and show a high degree of anaplasia and numerous mitotic figures. In the absence of any demonstrable primary tumor in the bronchi or in other organs, it is usual to designate this as a "mesothelioma of the

pleura." It has been the experience of the most exacting pathologists that a small primary tumor in a bronchus or in another organ such as the prostate can be found in these cases, denying the existence of a true mesothelioma of the pleura. Further study will be necessary before an exact answer can be given to this problem.

Changes in the Thorax Following Lobectomy, Pneumonectomy, and Pneumothorax

The space left upon removal of a lobe or an entire lung is filled with a clot of fibrin, which gradually undergoes organization to form a loose mass of fibrous tissue with numerous small spaces. The remaining lobes, or the opposite lung, expand and gradually compress the fibrous tissue so that it forms a part of the reconstructed thoracic wall. The heart becomes displaced, and in the case of pneumonectomy the opposite lung carries the mediastinum ahead of it, and finally fills the entire thoracic space. The individual alveoli and terminal bronchioles of the lung are dilated, but there is no loss of elastic tissue, and no destruction of the parenchyma of the lung (Rienhoff). After pneumonectomy in children there is probably an increase in the number of respiratory units of the lung (Bremer). Within a few weeks the respiratory gases in both the lung and the blood are entirely normal (Heuer and Andrus). There is no change in the esophagus following pneumonectomy except slight displacement toward the side that has been operated upon (Maier and Ehler).

After long-continued pneumothorax, there is slight to moderate fibrosis of the lung (Potter).

Foreign Bodies and the General Effects of Obstruction of the Lower Respiratory Tract—Organizing Pneumonia; Organizing Bronchiolitis

A great variety of foreign bodies have been found in the trachea and bronchi. From the standpoint of the pathologic changes produced by the foreign body, they are most logically divided into those which give off an

irritating substance, and those which are bland. The pathologic changes may then be divided into the direct effects of chemical substances within the foreign body, and the indirect effects of the foreign body in producing obstruction of a bronchus (Clerf).

Most foreign bodies introduced into the bronchi, such as teeth, parts of artificial dentures, bones, and coins, are bland. On the other hand, a common foreign body in children is the peanut, which contains chemical substances that are extremely irritating to pulmonary tissue. Within twenty-four hours after the aspiration of a peanut the surrounding pulmonary tissue shows edema, hemorrhage, and foci of bronchopneumonia, at times sufficiently severe to produce death.

Organizing Pneumonia. All foreign bodies in the bronchi and all lesions which bring about bronchial stenosis give the same general pathologic changes in the lung. These changes are manifold and include pneumonia, bronchiectasis, and abscess of the lung, but there is an additional distinctive lesion termed "organizing pneumonia."

A pyramidal focus of pulmonary tissue, corresponding to the distribution of the obstructed bronchus, is firm and gray. On section the architecture of the lung is completely obscured and replaced by an interlacing mass of gray fibrillar tissue. Within this gray tissue there are characteristic small, bright yellow foci. In addition there may be small or large abscess cavities or ectatic bronchi. The alveolar arrangement of the lung is in most areas still discernible. The alveolar walls are slightly thickened, but characteristically the alveolar spaces are filled with roughly round masses of young connective tissue. The alveolar and bronchiolar spaces which remain are lined with cuboidal epithelium. In some bronchi there is metaplasia of the epithelium to the squamous type.

Organizing Bronchiolitis. Occasionally following the inhalation of poisonous gases, and rarely as a sequela of an infectious bronchitis, the exudate within the bronchioles undergoes organization. Numerous small, elevated, grayish yellow nodules are seen on the cut section of the lung, which represent organization within the lumen of the smaller bronchioles. Clinically, there is intense dyspnea, since the lesion brings about an effective blockage of respiration (LaDue).

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LXXXIV

Congenital Cardiac Disease

Congenital cardiac disease is that condition in which, owing to disturbance of development or disease occurring in intra-uterine life, abnormalities exist in the anatomic structure of the heart or great vessels. Some of the abnormalities do not impair the ability of the heart to function, but do serve as foci for secondary disease. Other abnormalities impair the ability of the heart to do work, either through inadequate development of some part of the heart, or through a rearrangement of the circulation. When the rearrangement of the circulation involves a shunt of blood from the venous to the arterial side, there are serious consequences.

Causal Factors and Pathogenesis of Congenital Cardiac Disease. The basic structure of the heart is laid down between the fifth and eighth weeks of life, and it follows that any disturbance in the anatomic structure of the heart must act before the eighth week. German measles in the pregnant woman during the first two months is associated with congenital anomalies of the heart in the fetus (see section on Rubella, p. 374). Other conditions surrounding the developing embryo are more difficult to evaluate. In this category are disease of the amnion or chorion and defective nutrition through the placenta and the umbilical arteries. Finally, there is defective germ plasm, either isolated or familial. Congenital cardiac disease has been repeatedly recorded in siblings, but rarely in successive generations.

Incidence and Classification of Congenital Cardiac Disease. Definite congenital cardiac lesions are found in about 1 per cent of all autopsies. This is exclusive of the incidental guarded patency of the foramen ovale. Between 10 and 20 per cent of all cardiac disease in children is of the congenital type. From a

practical standpoint, congenital cardiac disease may be divided into three categories: (1) cases in which no abnormal communication exists and there is no cyanosis; (2) cases in which an abnormal communication exists with an arteriovenous shunt and possible transient or terminal reversal of flow; and in which cyanosis develops only under great strain or terminally (cyanose tardive); (3) lesions with an abnormal communication and a venous-arterial shunt, so that a part of the systemic blood in the aorta is venous, and there is persistent permanent cyanosis (morbus caeruleus).

Associated Lesions and Diseases. The greatest threat to the life of a person with a congenital cardiac lesion, especially a defect of the interventricular septum, a patent ductus arteriosus, or a bicuspid aortic valve, is subacute bacterial endocarditis. This disease usually develops in the twenties or thirties. The reasons for the localization of the bacteria are discussed fully under "Subacute Bacterial Endocarditis" (p. 720). This threat is so great that attempts have been made in the past few years to obliterate a patent ductus arteriosus by surgical ligation. The results are most encouraging. A complication of coarctation of the aorta, found in about one-fourth of all instances, is rupture of the aorta with hemorrhage into the mediastinum or into the pericardial cavity. For reasons not evident, about one-third of all patients with congenital pulmonary stenosis develop tuberculosis of the lungs. A point bearing on the pathogenesis of congenital cardiac disease is the rather close association of one defect, ostium atrioventriculare commune, with mongolism. It seems probable that the interference with development, resulting in the two conditions, occurs at the same time in fetal life.

Pathologic Anatomy

Coarctation of the Aorta. If the isthmus of the aorta is 8 mm. less in diameter than the arch, there is coarctation; that designated the "infantile type" is diffuse, and the adult type is sharp and annular. There is fibrosis of the wall at the constriction. Frequently associated lesions include hypoplasia of the aorta and

course of rheumatic endocarditis (Osler). Histologic study with serial sections through the raphe may give important data, as any remnant of the typical arrangement of the elastica at the raphe would indicate that the lesion is acquired (Lewis and Grant). There can be no doubt that bicuspid aortic valves may be congenital, but some are acquired (Gross and Fried).

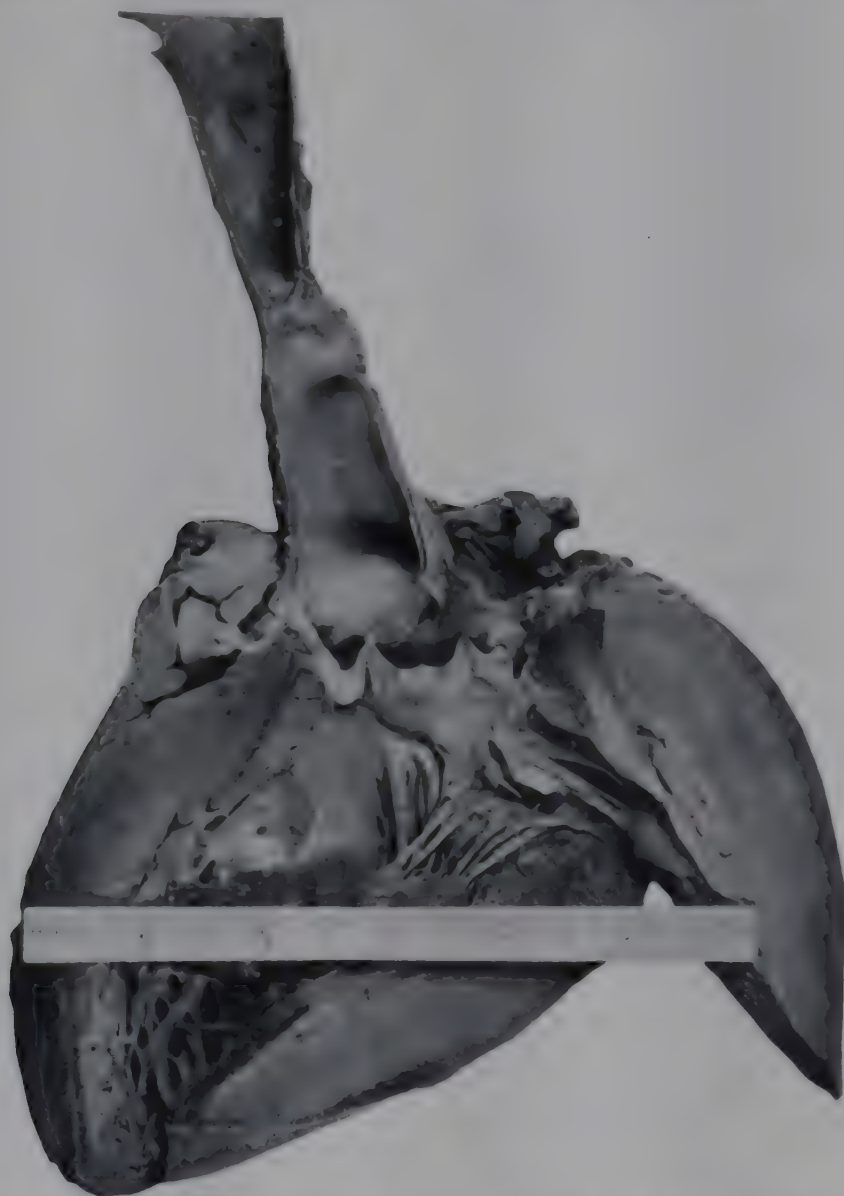


Fig. 341. Coarctation of aorta. (Armed Forces Institute of Pathology, Neg. No. 74113.)

bicuspid aortic valve. Collateral circulation around the constriction is extensive, especially the intercostal and internal mammary arteries which erode the ribs to give a characteristic change in the radiogram. The average age of death is thirty-five years and the commoner causes are rupture of aorta 23 per cent, bacterial endocarditis or aortitis 22 per cent, congestive failure 18 per cent, and an intracranial lesion 11 per cent (Reifenstein, Levine, and Gross).

Bicuspid Aortic Valve. This condition needs little description, and the only points of interest concern the relation to subacute bacterial endocarditis, and the possible formation of bicuspid aortic valves during the

Right Aortic Arch. Under certain conditions the right fourth branchial artery remains as the arch of the aorta with or without persistence of the normal left aortic arch. When both persist, the trachea and esophagus are enclosed in a vascular ring. There are no physiologic changes, but the roentgenologic appearance is characteristic.

Idiopathic Hypertrophy of the Heart. This term includes a variety of disease entities, some definite and others indefinite. The heart may be enlarged because of the accumulation of large amounts of glycogen within the fibers—von Gierke's disease—or because of some inflammation of the myocardium. Other cases cannot be adequately explained. Death is

likely to occur at any age up to four years. Dyspnea and cyanosis set in suddenly, and death ensues within a few hours or days.

Congenital Rhabdomyoma of the Heart. These are single or multiple tumors in the myocardium, composed of immature, striated muscle fibers. They are not infrequently associated with tuberous sclerosis of the brain, sebaceous adenoma of the bridge of the nose, and tumors of the kidney. It is not clear whether they represent true tumors or anomalies of development.

Patent Foramen Ovale. The patency of the foramen ovale during fetal life is necessary for viability, and premature closure leads to serious disturbance in the circulation. During the first few weeks after birth, under the influence of pulmonary activity, the flow of blood to the

atrium. Paradoxical embolism is the proof of these conclusions (Ingham). The association of an unguarded patent foramen ovale with mitral stenosis gives a fairly characteristic clinical and roentgenologic picture (McGinn and White). The essential pathologic findings in a defect of the interauricular septum (patent foramen ovale or defect of the septum primum) are great dilatation and hypertrophy of the right atrium and right ventricle, relative enlargement of the pulmonary artery and its branches, and a small left ventricle and aorta.

Persistent Ostium Primum. A defect in the septum primum near the atrioventricular valves may exist singly or in combination with a defect in the interventricular septum. In the latter instance there is a single large

TABLE 36. AGE IN RELATION TO ANATOMIC CLOSURE OF FORAMEN OVALE

Age	Total Number of Cases	Number of Cases Obliterated	Percentage of Cases Obliterated
Birth to 8 days.....	293	2	0.7
15 to 32 days.....	273	35	12.8
61 to 91 days.....	158	55	34.8
9 to 12 months.....	20	11	55.0
5 to 10 years.....	12	8	66.6
Over 20 years.....	1712	1228	71.7

lungs is steadily increased, and the volume and pressure in the left atrium is proportionally increased (Patten). The percentage of anatomic closure in relation to age is shown in Table 36 (Scammon and Norris).

In those adult hearts where the valvula does not completely cover the fossa there can be little doubt of an actual passage of blood from one atrium to the other, depending on relative pressures. This type might well be known as an “unguarded” patency of the foramen ovale. On the other hand in about 25 per cent of all hearts, the valvula completely covers the fossa, and a patency is evident only by passing a probe diagonally through the foramen. So long as normal physiologic conditions exist (greater pressure in the left atrium than in the right), this foramen is closed. But in failure of the heart with venous congestion, or in obstruction of the pulmonary artery, the pressure in the right atrium is increased, and the foramen allows the passage of blood and particulate matter from the right to the left

orifice between the two atria and the two ventricles, guarded by five valves, one of which, on the left side, is frequently bifurcated—ostium atrioventriculare commune.

Localized Defects of the Interventricular Septum. These defects are observed most frequently in the membranous portion of the septum. They are frequently the seat of subacute bacterial endocarditis, located either on the margins of the defect or on the endocardial surface of the right ventricle, against which the blood flows from left to right. Under normal conditions this anomaly leads to a shunt of blood from left to right, and there is therefore no cyanosis. Usually a loud murmur is heard, both anteriorly and posteriorly, produced by the rush of blood through the small defect. Defects in the muscular part of the interventricular septum are rare. The heart with a complete absence of the interventricular septum is termed “cor triloculare biatriatum.” Similarly, complete absence of the interauricular septum is designated as cor

triloculare biventriculare; and the absence of all septa is known as cor biloculare.

Patent Ductus Arteriosus. As in the case of the foramen ovale, the ductus arteriosus is a necessary part of the fetal circulation. The time of obliteration after birth is shown in Table 37 (Scammon and Norris).

At birth the vessel varies from 2 to 5 cm. in length and 1 to 10 mm. in diameter. The process of obliteration is essentially one of fibrosis of the media, contraction of the fibrous tissue, and final thrombotic occlusion. There are few symptoms in uncomplicated patency, and the only significant sign is a loud, continuous murmur. Subacute bacterial endocarditis not infrequently localizes in the patent ductus and on the wall of the pulmonary artery about the orifice. It would appear that surgical liga-

Tetralogy of Fallot. This complex anomaly, one of the commonest in adults, is made up of pulmonary stenosis, hypertrophy of the right ventricle, defect of the interventricular septum, and dextroposition of the aorta. Secondary changes in the lungs consist of great enlargement of the bronchial arteries, establishment of anastomoses between the bronchial and pulmonary arteries (Hales and Liebow), and widespread thrombosis of the smaller pulmonary arteries (Rich).

Transposition of the Great Vessels. In the development of the heart the primitive truncus is divided into two vessels, which then rotate through about 180 degrees, so that the systemic artery takes origin from the left ventricle. This rotation may fail, or it may be only partial, so that the systemic artery arises

TABLE 37. AGE IN RELATION TO OBLITERATION OF DUCTUS ARTERIOSUS

Age	Total Number of Cases	Number of Cases Obliterated	Percentage of Cases Obliterated
Birth to 8 days.....	311	1	0.3
15 to 22 days.....	143	16	11.2
46 to 61 days.....	57	27	47.4
91 to 120 days.....	63	52	82.5
120 to 365 days.....	89	84	94.5

tion of the patent ductus carries a lower percentage mortality than the percentage incidence of subacute bacterial endocarditis, and is therefore to be seriously considered as an operation of election during the second decade of life.

Defect of the Aortic Septum. Congenital Aneurysm of the Right Sinus of Valsalva. The septum in the primitive truncus arteriosus normally divides this large vessel into two equal parts. Occasionally, one vessel is larger than the other, and the latter is spoken of as "hypoplastic." Toward the base of the heart the septum may be deficient, and a fistula then exists between the aorta and the pulmonary artery. Rarely, the septum is abnormally thin in the region of the right sinus of Valsalva, and an aneurysmal sac forms.

Defect of the Interventricular Septum and Dextroposition of the Aorta. A defect in the fusion of the interventricular septum with the septum of the truncus arteriosus, together with inadequate rotation of the great arterial trunks, leads to this combined anomaly.

from the right ventricle. There are then two independent circulations, and the blood in the systemic vessels is completely unoxygenated unless there is a defect of one of the cardiac septa or a patent ductus arteriosus to bring some of the blood from the pulmonary circulation into the systemic circulation. In the absence of the anatomic basis for a shunt, the condition is incompatible with life.

Persistent Truncus Arteriosus. In the uncomplicated examples of this anomaly, a large common arterial trunk arises from the base of the heart above a defect in the interventricular septum. There are three, four, or five cusps. The pulmonary artery may arise from the common truncus a short distance above the valves or from the transverse or descending arch.

Coronary Arteries. Multiple origins of the coronary arteries, especially the right, are common and of no significance. Origin of one or both coronary arteries from the pulmonary artery leads to degenerative changes in the myocardium (Kaunitz). A single coronary artery has been observed.

Physiologic Considerations and Clinicopathologic Correlation

Congenital cardiac lesions lead to a variety of secondary changes in the size, shape, and position of the heart, in the pathway of the circulation, in the oxygen saturation of the blood, in the quality and quantity of the electrical excitation waves during contraction, and in hemodynamics. Available to the physician are many procedures to test these variations from the normal: physical examination, roentgenologic study, electrocardiographic tracings, and laboratory determinations. After six months, when the circulation becomes stabilized, and certainly after the first year of life, a definite attempt should be made to study the patient and arrive at a precise anatomic diagnosis.

Changes in the Size, Shape, and Position of the Heart. Percussion and auscultation of the heart may reveal these alterations, but roentgenograms are more valuable. The roentgenographic appearance of many lesions is characteristic, and a positive diagnosis is frequently possible. A few examples are: abnormal prominence of the pulmonic arch (patent ductus arteriosus); bluntness of the left lower contour of the heart—*coeur en sabot* or wooden-shoe heart (tetralogy of Fallot); and aortic knob on the right side (persistent right aortic arch) (Roesler).

Changes in the Pathway of the Circulation. In this category are abnormal communications between the venous and arterial circulations and the development of collateral circulation in stenotic or atretic lesions. The best example of the establishment of a collateral circulation is the roentgenographic demonstration of erosion along the lower margins of the dorsal part of the ribs by the enlarged intercostal arteries in coarctation of the aorta (Roesler). Abnormal communications are evidenced by thrills and murmurs (occasionally heard in utero), caused by the rush of blood through a small opening. A more precise demonstration of a change in the pathway of the circulation is given from a study of circulation times. For example, it is possible to measure the time which it takes for a substance to pass from the arm to the lung (with ether) and from the arm to the tongue (with saccharine). In a normal person the arm-tongue time includes the arm-lung time,

and is therefore considerably longer. If there is a significant venous-arterial shunt, the two times are in a ratio of about 1:1, instead of 1:2 or 1:3 (Benenson and Hitzig).

Changes in the Oxygen Saturation of the Blood. The presence or absence of cyanosis is determined by four influencing factors: (1) diminution of oxygenation in the lungs from alterations in the alveoli or from lowered oxygen tension of the expired air—*l* factor; (2) the direct entrance of an anomalous shunt of venous blood into the arterial stream through a defect— α factor; (3) increased deoxygenation at the periphery either through retardation of flow in the capillaries or through increased consumption of oxygen in the tissues—*D* factor; and (4) an abnormally high hemoglobin content—*T* factor. These factors commonly act in pairs *l* and *T*, and α and *D*. The latter combination is characteristic of most cases of cyanosis due to congenital cardiac disease. When the oxygen unsaturation of the arterial blood decreases by approximately 6.7 per cent, cyanosis appears. With these known factors it should be possible to calculate the amount of venous-arterial shunt according to the following formula:

$$\alpha = \frac{A-lT}{V-lT}$$

When *T*=total hemoglobin content of the blood, *A*=reduced hemoglobin content of arterial blood, *V*=reduced hemoglobin content of venous blood; α =fraction of total blood shunted through unaerated channels.

Further evidence on the inadequacy of the circulation to carry oxygen to the tissues is given by the finding of polycythemia, and by a determination of the blood lactic acid. In all venous-arterial shunts there is some degree of anoxemia. In an attempt to compensate for this, there is polycythemia. The amount of lactic acid in the blood stream is an index of the available oxygen in the tissues. The deficiency of oxygen in the peripheral circulation is reflected in a number of changes in the tissues. The retina takes on a characteristic dark hue, known as "cyanosis retinae." The capillaries at the extremities of the fingers and toes are dilated and show broad, long loops, and are different from the capillaries in cyanosis produced by a chronic acquired lesion. The

longstanding poor circulation in the extremities leads to the club fingers and club toes. There is proliferation of the periosteum of the bones with new bone formation, and hyperplasia of the fibroblasts in the subcutaneous tissue.

Changes in the Quality and Quantity of the Electrical Excitation Wave During Contraction. In only a few of the congenital anomalies of the heart is there a characteristic change in the electrocardiogram. Most patients with cyanosis show some alteration. In general the alteration consists of large voltage, axis deviations, diphasic QRS complexes, and abnormally high P waves (Katz and Wachtel; Eisenberg and Gibson). In dextrocardia the tracing in Lead I is a mirror image of the normal. In some of the cases of a defect of the interventricular septum and in ostium atrioventriculare commune, there is heart block caused by absence of the bundle of His (Yater, Barrier, and McNabb; Yater, Lyon, and McNabb).

Hemodynamics. In coarctation of the aorta there is a major obstruction to the flow of blood into the descending aorta. It follows that the systemic blood pressure in the vessels supplied from the arch of the aorta is higher than that in the blood vessels supplied from the descending aorta (Stewart and Bailey). The obstruction to the aorta is above the renal arteries, and there is therefore a certain degree of renal ischemia and generalized diastolic hypertension (Friedman, Seltzer, and Rosenblum).

Summary. The above methods and clinicopathologic correlations are not in themselves diagnostic, but by proper and judicious use of all of them a correct anatomic diagnosis can be made during life in well over one-half of all patients over one year of age with congenital cardiac disease (McGinn and White).

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Rheumatic Fever: Complications and Sequelae

Aside from the bacterial types of cardiac disease and nonspecific lesions of the heart in other conditions, most examples of clinical and anatomic disease of the heart can be arranged in four categories: (1) rheumatic heart disease (this chapter), (2) syphilitic heart disease (Chapter XL, p. 321), (3) the

tients, will serve to convey some idea of the general relations (Fig. 342).

Rheumatic Fever

The life story of rheumatic fever is a long one, beginning in childhood and ending in old age (Cohn and Lingg).

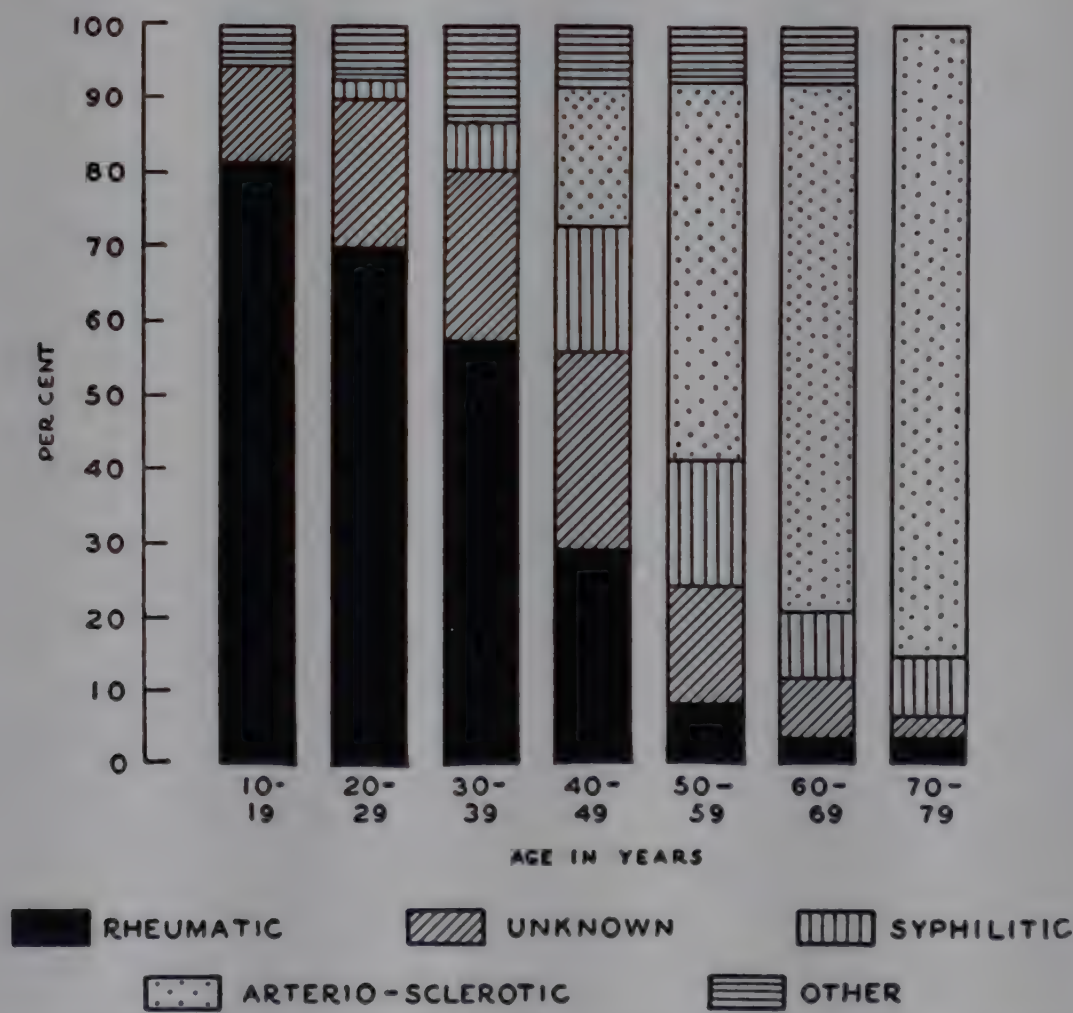


Fig. 342. Relative incidence of various types of cardiac disease in each decade. (Wilson: Rheumatic Fever. Commonwealth Fund.)

type of heart disease associated with disease of the arteries and hypertension (Chapter LXXXVI, p. 726), and (4) congenital heart disease (Chapter LXXXIV, p. 705). The relative incidence of the four varies according to the criteria used, and according to geographic location. One example, a clinical study combining both charity and private pa-

Initial Attack. On a day, most likely in the month of April, a seven-year-old girl complains of one of three manifestations: growing pains, chorea, or polyarthrititis. On the basis of known facts of incidence, this child is most likely a daughter of a moderately well-to-do industrial family, living in an urban community in a latitude and locality subject to

cold, rain, and wide fluctuations of temperature. At the time the child becomes ill there are likely to be no other cases of the disease in the family, although "epidemics" in institutions are occasionally observed (Ditkowsky, Stevenson, and Campbell). On the other hand, there is a good chance that one or more near relatives will give a history of having had the same disease as a child (Wilson, Schweitzer, and Lubschez).

Past History. There are no unusual features in the medical history of the child with rheumatic fever except that about one-third to one-half of the patients give a history of an attack of acute pharyngitis or tonsillitis caused by the hemolytic streptococcus from two to three weeks before the onset of the rheumatic manifestations. Some regard this as the inevitable association of two common diseases of childhood (Wilson), while others attach causal significance to it (Coburn).

Pathologic Anatomy of the Initial Manifestations. *Growing Pains.* The characteristic "growing pains" are in the hamstring tendons, which are tense, swollen, and tender on palpation. The pain is frequently referred to the front of the thigh and to the calf muscles, and the child may walk with a limp or with a bent knee to avoid tension on the involved structures. The essential change is acute tenosynovitis. Less common sites are the Achilles tendon and the muscles of the neck.

Polyarthritis. The involved joint is slightly swollen, red, hot, tender, and stiff. The synovia and periarticular tissue are edematous and congested. The synovial fluid is increased in amount and is slightly turbid. The synovial cells are hyperplastic, and in the surrounding tissue there are focal collections of mononuclear cells, single or in the form of Aschoff bodies. The endothelial and adventitial cells of the small blood vessels are prominent, and a few vessels are occluded by thrombi. The articular cartilage shows no change, and hence there is no permanent impairment of function. The ankles, knees, and wrists are most frequently affected.

Chorea. In spite of the prominent clinical signs and symptoms, pathologic changes of Sydenham's chorea are inconspicuous and inconstant. The brain is, in general, edematous and congested. In all parts, but especially in the basal ganglion, there are vascular thrombi, focal hemorrhages, perivascular in-

filtration with lymphocytes, and chromatolysis of the nerve cells. The localization responsible for production of the choreiform movements has been attributed to the superior cerebellar peduncle, the corpus luyisi, the optic thalamus, the red nucleus, and the putamen.

Whatever may be the anatomic basis and the physiologic mechanism, the clinical manifestations of chorea are definite. A previously well-behaved, lively, good-natured child becomes sulky, irritable, disobedient, inattentive, and clumsy. The irregular, uncoordinated movements, subjectively purposeful but objectively purposeless, are easily recognized. An attack lasts from a few to many months.

Course of Rheumatic Fever. Following the initial attack, either of two courses may be followed: no further attacks or recurrence. The latter event is well shown in a typical patient studied by Dr. May Wilson, from the age of thirteen to twenty-eight. During the sixth year there were chorea and polyarthritis; chorea in the seventh year, extending into the eighth; polyarthritis in the ninth; both polyarthritis and chorea in the twelfth; chorea, polyarthritis, and joint pains in the thirteenth; polyarthritis and active carditis in the fourteenth; joint pains in the fifteenth and sixteenth; joint pains and polyarthritis in the seventeenth; joint pains and probable carditis in the twenty-third; polyarthritis, erythema, and subcutaneous nodules in the twenty-fifth; and polyarthritis and subcutaneous nodules in the twenty-sixth. Cardiac involvement was first discovered at the age of six. At thirteen the heart was slightly enlarged, and there were signs of mitral stenosis and insufficiency. By the age of twenty-three the heart was enormously enlarged, and auricular fibrillation had set in. At twenty-six signs of aortic insufficiency were present. During the fifteenth and eighteenth years there were periods of cardiac decompensation, and following a second pregnancy in the twenty-second year severe cardiac failure was present from which a complete recovery was not made.

This case is of course an extreme example, but illustrates the manifold manifestations, the multiplicity of recurrences, and the progressive cardiac damage. The frequency of recurrences diminishes after puberty, and the majority of children who survive to puberty without manifest cardiac disease are free of symptoms during adolescent and young adult life.

Fate of the Child with Rheumatic Fever. In an average eight-year period following the first attack of rheumatic fever with active manifestations in the heart, 40 per cent of patients die, largely as the result of cardiac failure. If there has been only one attack of rheumatic carditis, the mortality is 20 per cent while if there are four or more attacks the death rate is 60 per cent. In contrast, those with slight or no evidence of cardiac involvement show a mortality in the following ten years of less than 1 per cent.

sue to the causal agent or agents of rheumatic fever is the Aschoff body. The initial change in the tissues is the appearance of "fibrinoid," a homogeneous eosinophilic acellular material. It was originally postulated that fibrinoid was a precipitation and inspissation of fibrin or a swelling and necrosis of collagen. However, histochemical studies clearly demonstrate that it is actually a precipitation of the acid mucopolysaccharide of the ground substance of connective tissue (Altshuler and Angevine). The focus is oval or spindle-shaped.

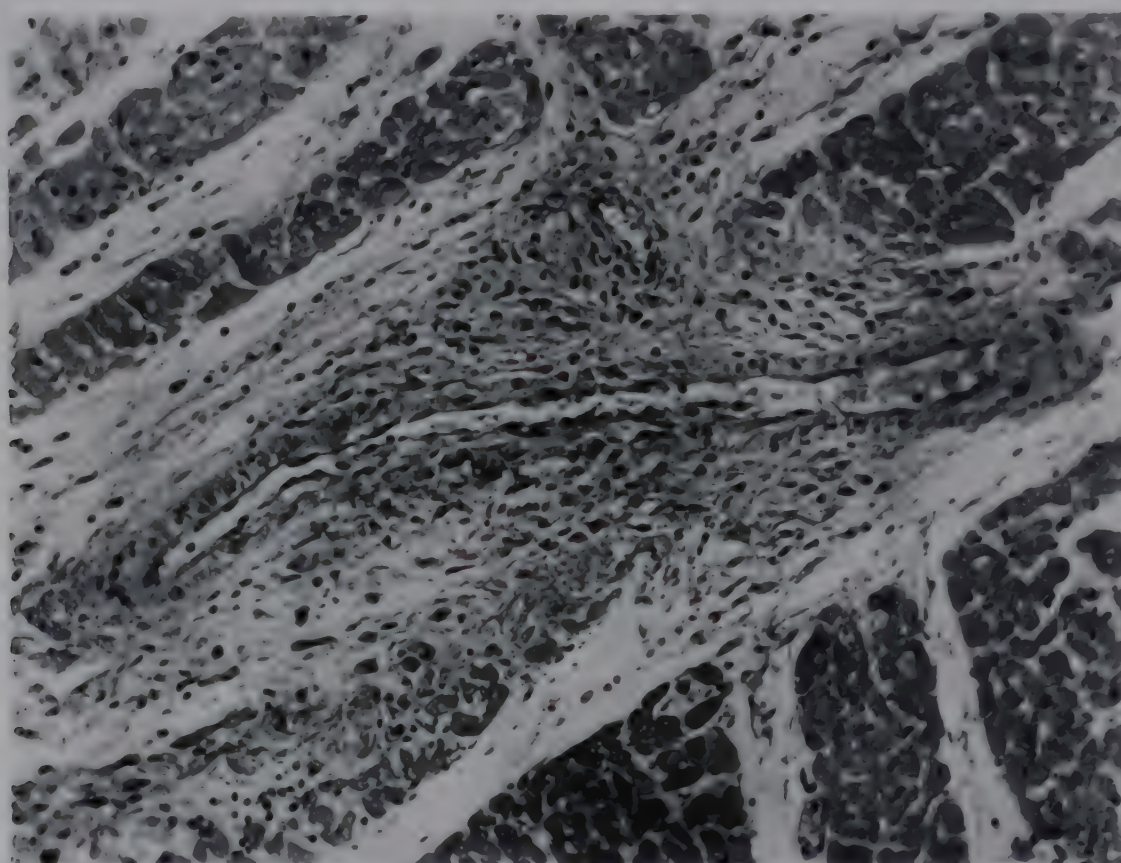


Fig. 343. Aschoff body in myocardium.

The average duration of life following an attack of rheumatic fever with carditis is about fifteen years. Approximately 2 per cent of all patients die by the end of the first year, 10 per cent by the end of the fifth, and 30 per cent by the end of the tenth.

Of those who survive into adult life, some develop subacute bacterial endocarditis during the third or fourth decade, and others have the signs and symptoms of chronic valvular disease and die of cardiac decompensation in the fourth, fifth, or sixth decade. These two—subacute bacterial endocarditis and chronic valvular disease—constitute a complication and a sequela respectively, and will be discussed later in this chapter.

The Reaction of the Tissues. The Aschoff Body. The characteristic reaction of the tis-

Fragmentation of the mass may be observed. At about the same time a few cells, slightly larger than lymphocytes, with a dense chromatic nucleus and scant cytoplasm, collect about the periphery of the swollen collagen. In the heart the myocytes, specialized mesenchymal cells found only in the heart, become conspicuous throughout the interstitial tissue (Clawson). Other cells soon appear within the nodule, known as "Aschoff's cells." These cells are large, with a prominent vesicular nucleus, containing a barlike or round central nucleolus. The cytoplasm is abundant, basophilic, and irregularly outlined. Multinucleated cells are frequently seen. As healing proceeds, the cells elongate and appear as fibroblasts. Between the cells a network of reticulin fibers is deposited. Finally, all evidence of previous

change disappears, and a small focus of scar tissue remains (Gross and Ehrlich; Klinge; Clawson).

So far as can be determined, the Aschoff body with the distinctive features of swollen collagen, polymorphous cells with ragged edges and typical nuclei and nucleoli, and reticulin network, is not observed in any disease except rheumatic fever. The time interval for the life history of the Aschoff body is difficult to determine, but several lines of

tended with a cloudy fluid, averaging 300 cc. in amount. The surfaces are covered with a fine fibrinous exudate. In the tissues are edema, hyperemia, and infiltration with lymphocytes, leukocytes, and occasional Aschoff bodies. As healing progresses there is organization of the exudate, and all variations from slight focal fibrous thickening of the pericardium to complete fibrous obliteration of the pericardial sac are seen. One of the favorite sites for minimal lesions is the atrioven-

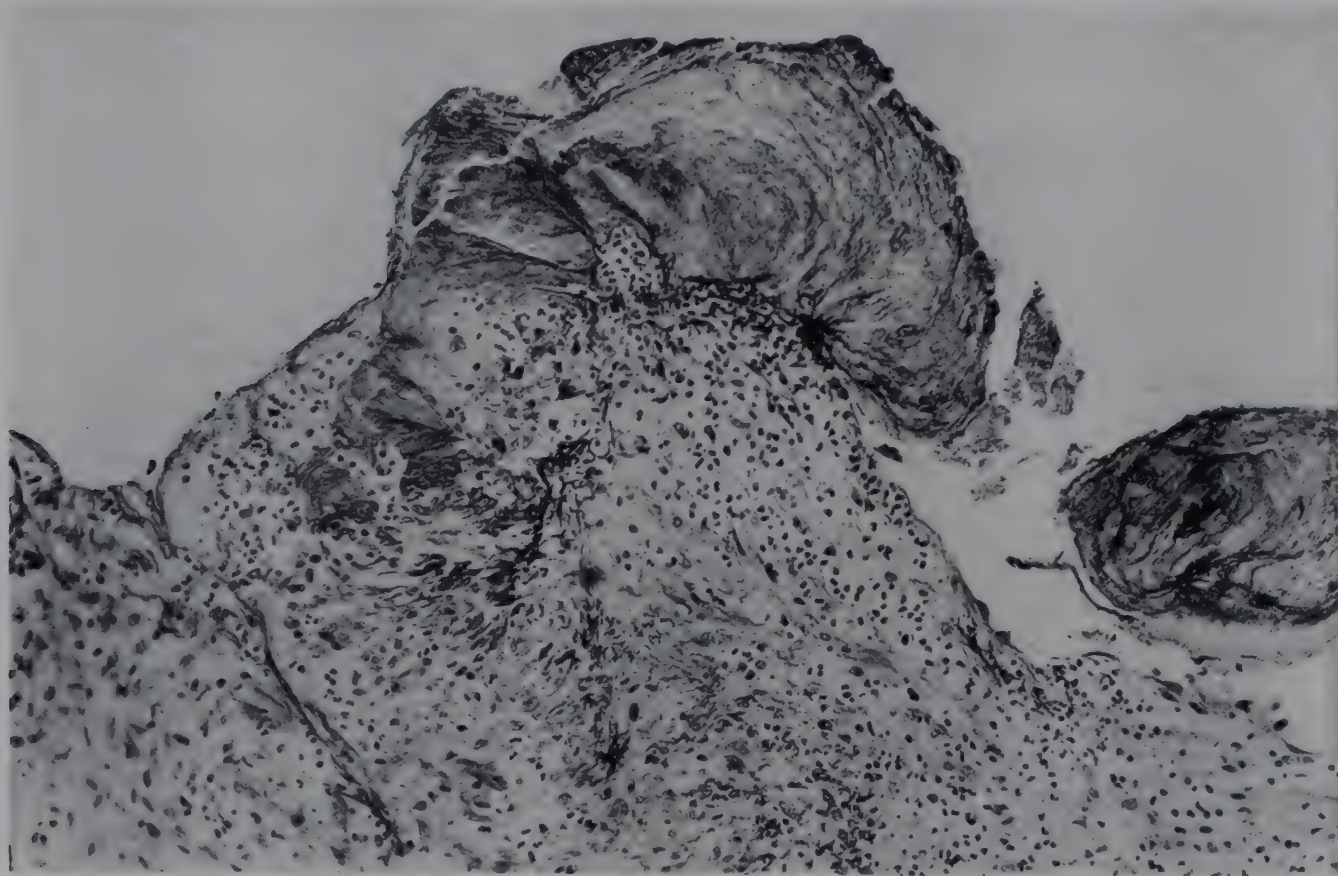


Fig. 344. Verruca on mitral valve in rheumatic fever.

evidence suggest that the period is four to six months (Gross and Ehrlich; Console).

Pathologic Anatomy. In any discussion of the pathologic anatomy of rheumatic fever, the names of those pathologists who have over the years contributed to our knowledge should be mentioned: Coombs, Aschoff, Gross and his associates, Klinge, MacCallum, Pappenheimer, and von Glahn.

Heart. All parts of the heart are involved, and it is customary to speak of "rheumatic pancarditis." In the acute stages the heart is of normal size or slightly enlarged, mainly as the result of dilatation, but with repeated attacks the heart is both dilated and hypertrophic. In children the hypertrophy is out of proportion to the amount of valvular damage, and it must be assumed that it results from the associated myocarditis.

PERICARDIUM. The pericardial sac is dis-

tricular groove, where delicate fibrous adhesions may be identified.

Occasionally, the inflammation extends to the outer surface of the pericardium, and there are adhesions to the pleura, and fibrous thickening of the anterior mediastinal structures.

MYOCARDIUM. The myocardium is pale, soft, and flabby. In an acute phase, small gray nodules may be seen, representing the Aschoff body. In recurrent attacks small foci of fibrosis are observed. As outlined in a preceding paragraph, the characteristic Aschoff bodies are present in the perivascular connective tissue and occasionally in other locations. The sites of predilection are the interventricular septum and the base of the posterior wall of the left ventricle. Less common sites are the wall of the left auricle, the left posterior papillary muscle, and the pulmonary conus (Gross and Ehrlich). In the conduction system there

are degenerative changes, cellular infiltration, and occasionally Aschoff's bodies—lesions which are quite adequate to explain the prolongation of the P–R interval and disturbances in the QRS complex, demonstrable clinically during an acute phase of rheumatic fever (Gross and Fried).

ENDOCARDIUM. Lesions of the endocardium may be found in any part of the heart, but are most frequently observed in the valves and in the endocardium of the left atrium. The typical lesions during the earliest stage are edema and cellular infiltration of the entire

valve is thus thickened and becomes firmer than normal. With repeated attacks the picture to be described later under "Chronic Valvular Disease" is produced. In the valvular rings there is intense inflammation, characterized by edema, congestion, infiltration with lymphocytes and mononuclear cells and the formation of Aschoff's bodies.

Blood Vessels. In both the larger and the smaller blood vessels there are distinctive lesions in rheumatic fever. In the aorta these appear as yellow, elevated nodules and streaks. The change is essentially one of in-

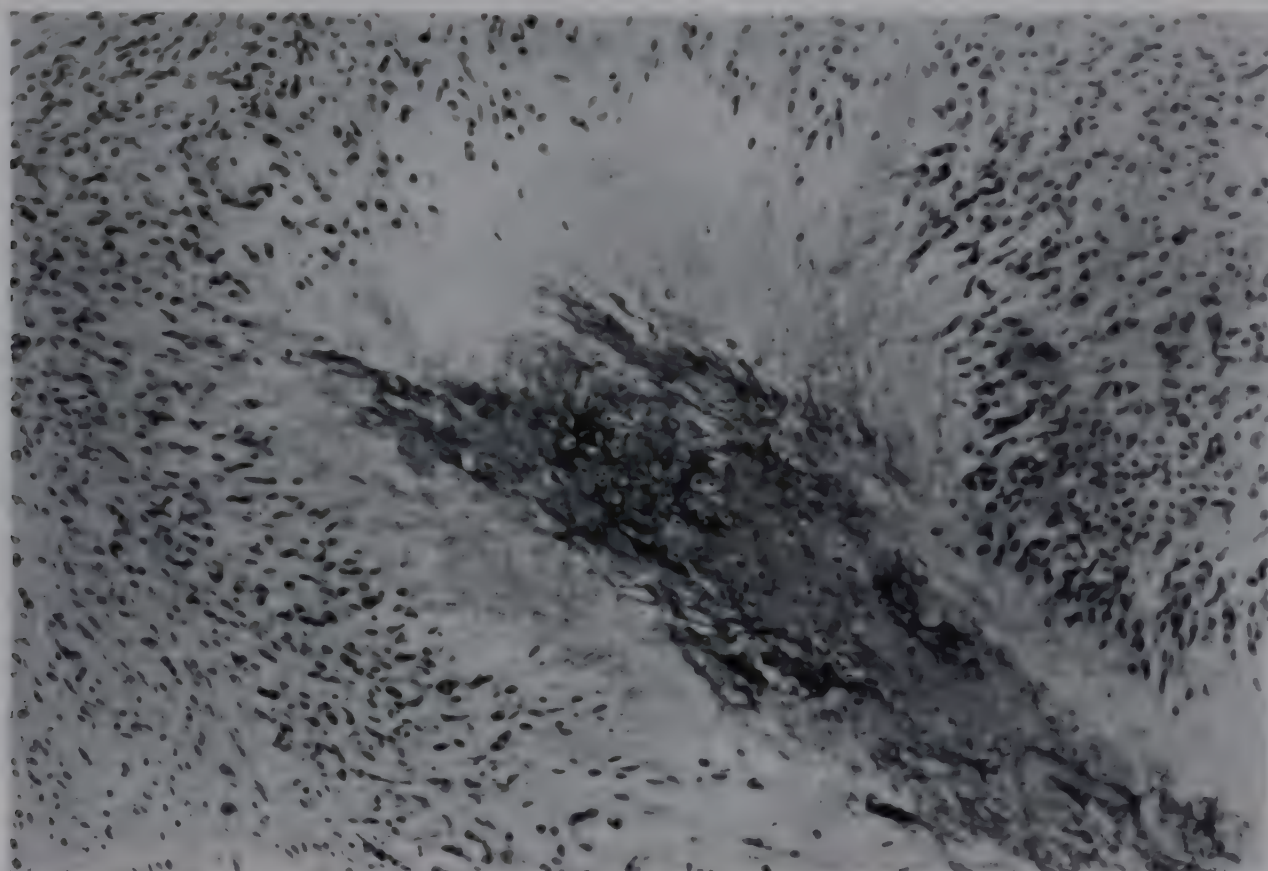


Fig. 345. Subcutaneous rheumatic nodule. (Armed Forces Institute of Pathology, Neg. No. 73941.)

valve; that is, true valvulitis. Soon thereafter verrucous endocarditis appears. The verrucae are first apparent as a subendothelial change along the line of closure of the valves as swelling of collagen and slight cellular infiltration. The endothelium is lifted and undergoes necrosis. There is then deposited on the surface a small thrombus which is firmly adherent to the tissues. The verrucae vary from 1 to 3 mm. in diameter, and are firm and reddish gray. Similar lesions are seen over the chordae tendineae of the auriculoventricular valves and on the endocardium of the left atrium above the posterior leaflet of the mitral valve (Gross and Friedberg; MacCallum). With healing there is proliferation of fibroblasts within the valve, and the blood vessels from the ring extend outward to the line of closure. The

inflammation, with cellular infiltration about the smaller vessels of the adventitia and media, and the appearance of Aschoff's cells and Aschoff's bodies (Pappenheimer and Von Glahn). In the coronary arteries there are similar lesions, and it has been observed that intimal arteriosclerosis is far commoner in those who have had rheumatic fever than in those who have not had the disease (Karsner and Bayles).

Lungs and Pleura. In addition to the accumulation of fluid in the pleura as a part of cardiac failure, acute fibrinous pleurisy may be an integral part of rheumatic fever. The lung shows atelectasis and passive congestion, and in some cases a focal interstitial inflammation and hemorrhage characterized by fibrinous hyaline thrombi in the capillaries,

hyaline membranes in the alveoli, and slight infiltration with leukocytes. In late stages there is organization with the formation of Masson bodies (Rich and Gregory; Olesen).

Subcutaneous Nodules. In some patients, especially children, small, firm nodules form in the subcutaneous tissues (Hayes and Gibson). They are loosely attached to the tendon sheaths, periarticular ligaments, superficial aponeuroses, or periosteum. The commonest sites are about the elbow, knee, ankle, and on the neck. They are composed of three layers: a central necrotic zone, a midzone of stellate and spindle-shaped cells frequently arranged radially, and a peripheral zone of congestion, edema, slight fibrosis, and cellular infiltration with lymphocytes. There is no change in the overlying skin. The appearance is similar to if not identical with that of the subcutaneous nodules of rheumatoid arthritis (Keil). Other lesions of the skin include purpura and erythema nodosum.

Lesions of Other Tissues. Inflammatory lesions, specific or nonspecific, of many tissues and organs have been described in rheumatic fever. Obscure abdominal complaints may be related to changes in the smaller blood vessels similar to or identical with those of polyarteritis nodosa (Gross and Friedberg). In the lymph nodes there are hyperplasia and hyperemia. A peculiar peripheral fatty degeneration and necrosis of the liver has been described by Wilson. The kidney shows no rheumatic lesions, but in an occasional patient acute glomerulonephritis is a complication.

Relation to Hypersensitivity. It has been suggested by many that rheumatic fever is the effect of a hypersensitivity to bacterial products, specifically to those of the hemolytic streptococcus. All attempts to produce the typical lesions of rheumatic fever in animals with bacteria and bacterial products have failed. However, Rich and Gregory and others have observed cardiac lesions "that in their basic characteristics resemble closely those of rheumatic fever" in rabbits subjected to anaphylactic hypersensitivity by injection of foreign serum. Further evidences for this view are the similarity of rheumatic pneumonia and experimental anaphylactic pneumonitis (Gregory and Rich), the occurrence of lesions of polyarteritis nodosa in rheumatic fever, and the similarity of serum sickness and rheumatic fever in man.

Subacute Bacterial Endocarditis

Subacute bacterial endocarditis is a definite clinical, pathologic, and etiologic entity. It represents the final illness in about 4 per cent of all persons who have had rheumatic fever, and it is an important cause of death in patients with congenital cardiac disease who live into young adulthood.

Pathologic Anatomy. The general pathologic changes in subacute bacterial endocarditis are those of an inflammatory reaction without necrosis and without suppuration. This may be caused by either the low virulence of the invading organism or the relatively high resistance of the host.

Cardiovascular System. The heart is usually of moderate size—400 to 600 gm. The pericardium may be thickened or show adhesions. The involved valve, mitral or aortic most frequently, is thickened, grayish white and opaque. The chordae tendineae are thickened and shortened. Vegetations, on the valve or auricular endocardium, are of moderate size, firm, and grayish yellow. On section the vegetation is composed of a basal layer of organization, a central mass of necrotic tissue, and a superficial layer of fibrin in which are large bacterial colonies. The myocardium is pale and frequently shows fatty degeneration and focal accumulations of leukocytes or frank abscesses (Saphir, Katz, and Gore). The arteries may show mycotic aneurysms (p. 720).

Other Organs. In the *lungs* there is slight to moderate chronic passive hyperemia, and not infrequently terminal bronchopneumonia. The *spleen* is consistently enlarged and weighs between 300 and 600 gm. It is firm, grayish red, with inconspicuous malpighian bodies. Throughout the spleen there are numerous infarcts caused by embolism arising from the valvular vegetations (Fig. 347). The *liver* is slightly enlarged and shows slight to moderate chronic passive hyperemia. The hepatic cells may show cloudy swelling or even central necrosis.

The *kidneys* are typical, and the diagnosis may frequently be made from gross and microscopic examination of the kidneys. They are slightly enlarged. The capsule strips with ease, leaving a smooth, slightly reddened surface. Within the cortex there are numerous petechiae. The cortex is slightly increased in thickness. There are no consistent changes in

the medulla or in the pelvis. The tubular epithelium is swollen and irregular. Within individual glomeruli single lobules are necrotic and infiltrated with leukocytes. The capillaries of these lobules are filled with hyaline thrombi. Within the capsular space there are red blood

per cent of glomeruli show this lesion, hence the name *focal*.

The *lymph nodes* throughout the body are enlarged and soft, and show hyperplasia with partial exhaustion of the lymphoid tissue. In the *skin*, in the *conjunctiva* and *mucous mem-*

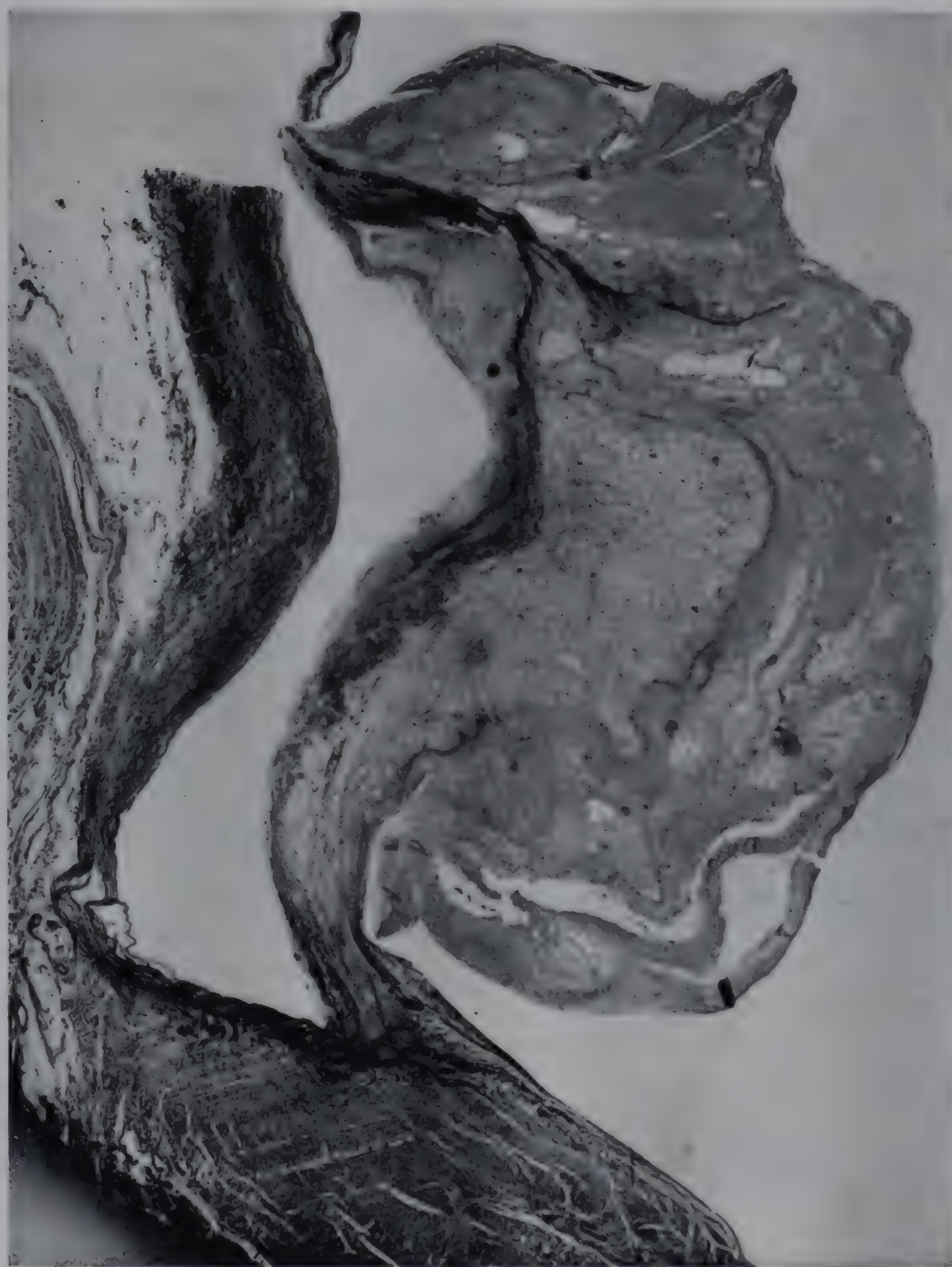


Fig. 346. Vegetation in subacute bacterial endocarditis. (Criteria of Heart Disease, American Heart Association.)

cells. This lesion is designated as "acute focal embolic glomerulonephritis," and probably does not occur in any disease except subacute bacterial endocarditis. Healing is accomplished by proliferation of the surrounding epithelium and the deposition of collagen, resulting in conversion of single lobules into small fibrous masses, adherent to the surrounding capsule—healed focal embolic glomerulonephritis (Fig. 348). Not over 5 to 10

branes, in the *gastro-intestinal tract*, and in the *urinary tract*, petechiae and ecchymoses are common. In the *brain*, changes are inconstant. Formation of a mycotic aneurysm with rupture and subarachnoidal hemorrhage has already been mentioned. Small emboli may result in focal meningitis or in numerous small abscesses of the cerebral substance (Kerkhof and Giere; de Navasquez; Knoll).

Healing. Before the use of the antibiotics a

rare example was seen at autopsy in which there was definite partial healing of a sub-acute bacterial endocarditis (Libman). In patients treated with adequate amounts of pen-

other bacteria, notably the gonococcus (Jones).
Incidence. From 80 to 90 per cent of all patients with subacute bacterial endocarditis are between the ages of eleven and forty years.

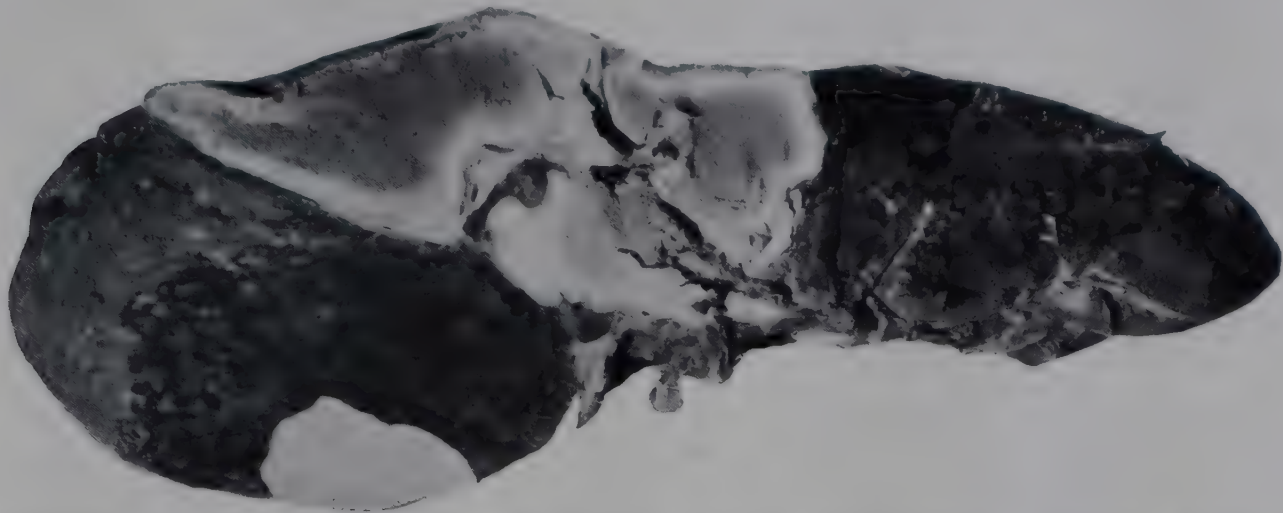


Fig. 347. Enlargement and infarct of spleen in subacute bacterial endocarditis. (Armed Forces Institute of Pathology, Neg. No. 63552.)

icillin, there is calcification of the center of the vegetation and organization of the superficial layers, at times indistinguishable from what has been recognized for many decades as calcific stenosis of the aortic or mitral valve (Moore).

It is slightly commoner in men than in women, in a ratio of 6:4. In over 90 per cent of instances the mitral or aortic valve, or both, are involved. Lesions of the mitral valve alone or of the mitral valve and the aortic valve constitute 80 per cent of all cases.

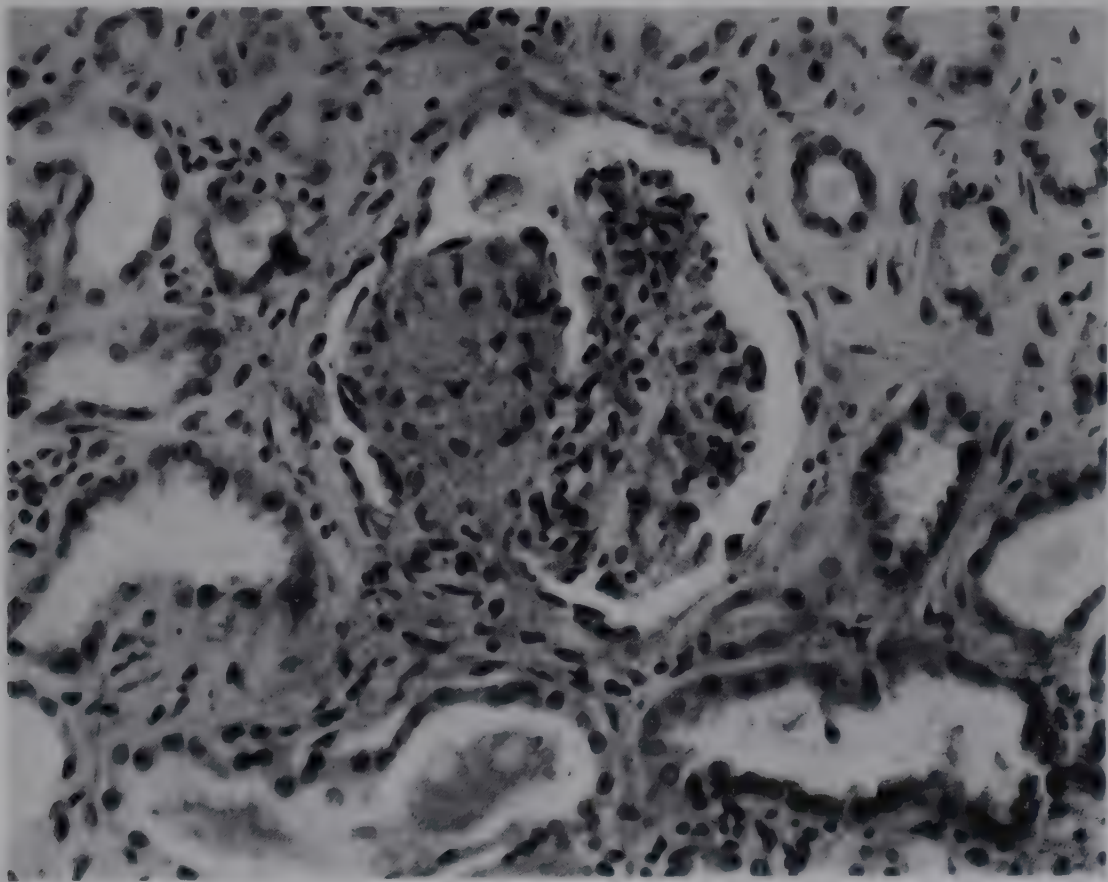


Fig. 348. Healing focal embolic glomerulonephritis.

Bacterial Causes. In general about 95 per cent of cases are caused by *Streptococcus viridans* (Solowey), 3 to 4 per cent by the influenza bacillus and 1 to 2 per cent by all

Portal of Entry of the Bacteria. Relation to Previous Cardiac Disease. The portal of entry of the bacteria can be determined in only about 20 per cent of instances. In these there

is usually a history of an upper respiratory infection or the extraction of a tooth. In about 50 per cent of patients there is a remote history of rheumatic fever, chorea, or repeated attacks of tonsillitis. In about 10 per cent there is some preexisting congenital lesion of the heart.

Clinicopathologic Correlation. The signs and symptoms in subacute bacterial endocarditis are dependent, as in all endocarditides, upon mechanical factors, the presence of infection, and the phenomenon of embolism. Mechanical interference with the function of the valves is an inconspicuous feature, and chronic passive congestion of the viscera is only slight or moderate. Auricular fibrillation or flutter is rare (Segal). The signs of infection are the characteristic swinging temperature curve, weakness, and night sweats. The leukocyte count is rarely above 15,000. However, damage to the bone marrow with suppression of both myelopoietic and erythropoietic activity is reflected in the characteristic anemia. This anemia leads to paleness of the skin and mucous membranes, and fatty degeneration of the myocardium. It may contribute also to the weakness and easy fatigability. The signs secondary to embolism are the most important in the clinical diagnosis of subacute bacterial endocarditis. Miliary emboli result in petechiae of the skin, mucous membranes, and conjunctiva; and in the lesion of the kidney—acute focal embolic glomerulonephritis. Necrosis of a part of the glomerulus results in hemorrhage in the glomerular capsular space and the appearance of red blood cells in the urine. Larger emboli produce infarcts of the spleen and kidneys, with symptoms of pain over these areas. Infarction of the spleen is also in part responsible for the characteristic enlargement of this organ. Emboli to the cerebral vessels with infarction result in a variety of neurologic signs, notably hemiplegia. Rupture of a blood vessel with a mycotic aneurysm is not an uncommon type of death (Blumer).

The Association of Subacute Bacterial Endocarditis and Congenital Anomalies of the Heart. In about 10 per cent of all cases of congenital anomalies of the heart in young adults there is an associated subacute bacterial endocarditis. It is commonest with bicuspid aortic valves, patent ductus arteriosus, and a defect of the interventricular septum. It is rare

with defects of the auricular septum (Abbott). It has been suggested that the high incidence of association with bicuspid aortic valves is related to the fact that this disorder is really rheumatic and not congenital (Gross).

Relation of Rheumatic Fever to Subacute Bacterial Endocarditis. In over three-fourths of instances of subacute bacterial endocarditis there is definite clinical and pathologic evidence of rheumatic fever, with damage to the cardiac valves. The two diseases have been observed together (Libman), and the finding of Aschoff's bodies in the myocardium in subacute bacterial endocarditis has been reported in proportions as high as 45 per cent (Clawson; Saphir and Wile; Von Glahn and Pappenheimer). It would seem that previous damage to the valves, such as by the presence of unhealed rheumatic verrucae (Von Glahn and Pappenheimer), or the fibrous deformity of the valve (Gross and Fried), may serve to anchor bacteria to the surface. There is also the factor of the hydrodynamics of the blood, in that the line of closure is subject to damage to a greater extent than other parts, and thus the vegetations are found in this area. An association with syphilitic valvulitis is unusual (Koletsy).

Subacute Bacterial Endarteritis. Vegetations identical with those formed on the cardiac valves are seen on the endarterium, particularly in association with arteriovenous aneurysm (Hamman and Rienhoff), coarctation of the aorta (Hamilton and Abbott), or patent ductus arteriosus. In the first and last the vegetations are located so that the embolism occurs into the lungs, and under these conditions suppuration, with the formation of multiple abscesses, is the rule.

Mycotic Aneurysms. A mycotic aneurysm is one caused by bacterial inflammation of the wall of an artery. The bacteria may be brought to the wall from within or from without. The former type is frequently known as an "embolic aneurysm." In 90 per cent of instances of mycotic aneurysm there is associated endocarditis, and in almost all of these the lesion of the endocardium is the specific condition, subacute bacterial endocarditis. Mycotic aneurysms are found in about 10 per cent of all instances of this condition. They are rare in other forms of bacteriemia, but have been reported in association with suppurative inflammation of the lungs and of

bone, and in polyarteritis nodosa (Klotz). The aorta is most frequently involved, with the superior mesenteric, hepatic, splenic, cerebral, and coronary arteries following in that order. The wall of the artery, except in the immediate vicinity of the aneurysm, is usually normal. The intima and the greater part of the media are completely destroyed. There is infiltration with polymorphonuclear leukocytes, and not infrequently foci of suppura-

disease," the valves are no longer able to close the orifice or to open completely, and the physiologic result is regurgitation (insufficiency) and stenosis respectively (Karsner).

Changes in the Valves. Five basic changes are responsible for the deformity of the valves: (1) marginal fusion, (2) fibrosis, (3) retraction, (4) fibrous union of the leaflet to the wall, and (5) shortening of the chordae tendineae.

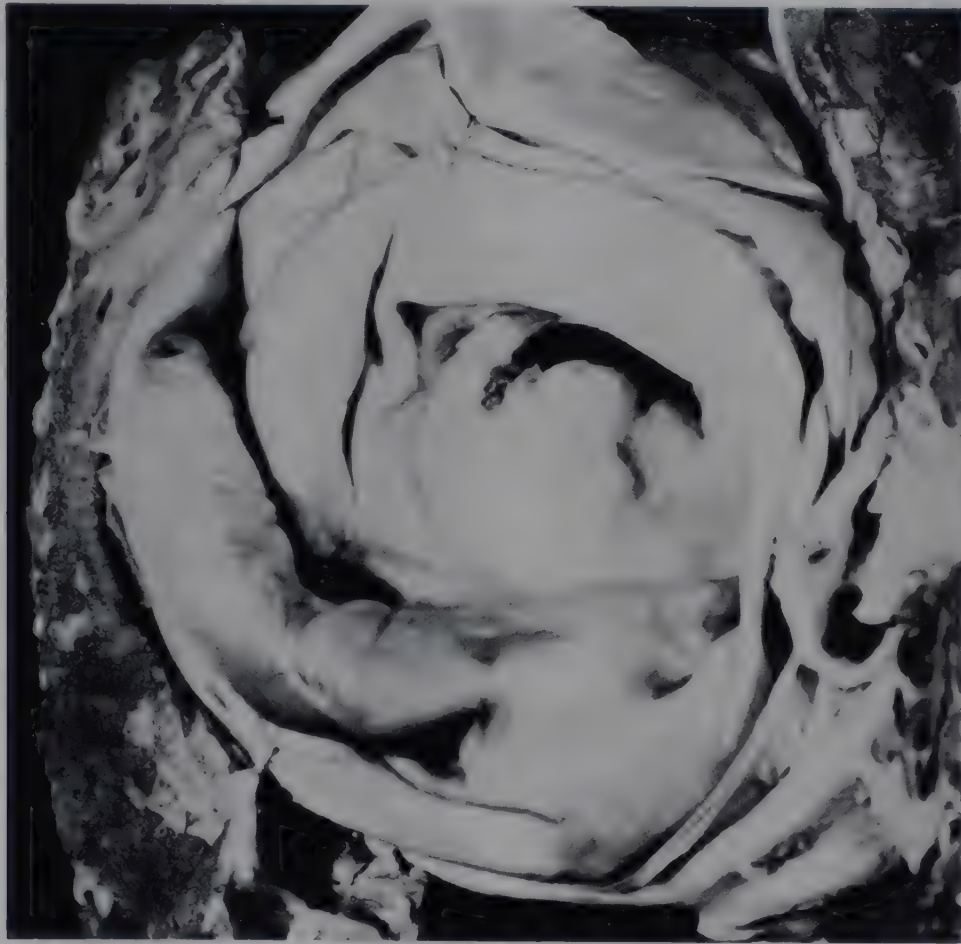


Fig. 349. Chronic endocarditis of mitral valve with stenosis viewed from above.

tion. The sacs rarely reach a size of over 3 cm. and are thin-walled. Rupture into the surrounding tissue, and even the formation of a false aneurysm, is common. There is little clinicopathologic correlation beyond those signs and symptoms resulting from massive hemorrhage into the tissues with pain and a palpable mass, if it is near the surface of the body (Stengel and Wolferth).

Chronic Valvular Disease

The four valves of the heart guide the flow of blood and allow a periodic ejection into the two arterial systems. Their function depends on the preservation of the normal anatomic structure—a smooth pliable membrane, adequate in size to close the orifice.

Pathologic Anatomy. In the condition known as “chronic endocarditis,” “chronic deforming valvulitis,” or “chronic valvular

MARGINAL FUSION. Marginal fusion is seen in the semilunar valves as an adherence of the leaflets to one another at the commissure. Normally the two leaflets arise independently, but in chronic endocarditis there is a single extension of tissue for a distance of 1 to 5 mm. before the division into the two valves. The same change is observed in the atrio-ventricular valves. Instead of two or three separate leaflets, there is a single circular membrane with an orifice in the center.

VALVULAR FIBROSIS. This needs little explanation. The thin, transparent, normal valve becomes a thickened, opaque, firm, nonpliable structure, which cannot respond to the alternating pressures on the two sides. A secondary effect of the fibrosis is a rolling of the free edge of the semilunar cusps generally toward the wall in chronic endocarditis, and toward the lumen, in syphilitic valvulitis.

RETRACTION. The same fibrosis is responsible for retraction. The valve is held at the valvular ring, and is entirely free toward the lumen. Hence any contraction of scar tissue must pull toward the ring and shorten the leaflet. For normal function of the atrio-ventricular valves the linear distance from the ring to the line of closure must equal the radius of the orifice. Similarly the length of the line of closure of the semilunar cusps must be at least twice the radius of the orifice. A shortening of the valve or a dilatation of the ring will result in failure of union of the closed cusp, and consequent insufficiency.

FIBROUS UNION OF CUSP TO WALL. This is seen especially in syphilitic aortic valvulitis. The commissure is split apart by a plaque in

TABLE 38. VALVULAR INVOLVEMENT IN CHRONIC ENDOCARDITIS, 130 CASES

Valves	Total	Alone
Mitral.....	95	44
Aortic.....	82	32
Tricuspid.....	13	0
Pulmonic.....	3	3
Mitral and aortic.....	50	—

the aortic wall, and the first few millimeters of the valve are sealed to the aorta.

SHORTENING OF CHORDAE TENDINEAE. The chordae tendineae of the auriculoventricular valves are a source of added damage. The chordae prevent the intraventricular pressure from forcing the leaflets into the atria, but they must be sufficiently long to allow the valves to meet. With fibrosis, thickening, and adherence of the chordae, there is contraction and shortening. The valves already converted into a thick, perforated diaphragm are pulled toward the ventricles—buttonhole valve, funnel valve. The opposite state, in which a chorda ruptures and permits a leaflet to float freely in the blood, is a rare complication of acute or subacute endocarditis (Gelfman). The resulting insufficiency comes on suddenly, and the murmur is usually extremely loud.

FIBROSIS OF FIBROSA AND SPONGIOSA. The normal valves are covered by a fibroelastic tissue, enclosing a centrum of fibrous tissue. The latter is differentiated into a loose layer, the spongiosa, toward the surface over which the blood flows, and a dense layer on the opposite side—the fibrosa (Gross and Kugel).

In chronic endocarditis there is diffuse fibrosis, more extensive in the spongiosa. There are numerous thin-walled sinusoids and only rarely any significant infiltration with wandering cells.

Inconstant but important changes include diffuse or nodular *calcification* within the fibrotic leaflet, and *ulceration* of a calcified nodule with thrombosis at the site. Locking of the calcified nodules may be the cause of unexpected death (Clawson, Noble, and Lufkin).

Changes in the Adjacent Mural Endocardium. In chronic endocarditis of the mitral valve the mural endocardium in the posterior-inferior region of the left atrium may be focally thickened and hollowed out so that there are openings directed toward or away from the valve. These are pockets of insufficiency and of stenosis respectively. They probably represent response to mechanical stresses within the cavity.

Changes in the Valvular Rings. The valvular rings in most examples of chronic endocarditis show an increase of fibrous vascularized tissue and slight lymphocytic infiltration.

Changes in the Cavities and in the Myocardium. The insufficiency or stenosis alters the pressure and volume relations in the separate cavities of the heart, and dilatation and hypertrophy result. In stenosis there is likely to be eddying of the blood behind the stenotic orifice, and consequent thrombosis, usually in the atrial appendages. Rarely, a thrombus may become free in the atria—ball thrombus—and sudden impaction of it into the orifice is a cause of unexpected death. Thrombosis within the ventricles is less common.

Incidence of Valvular Involvement. The valves of the left side of the heart are affected more frequently than those of the right side, as shown in Table 38 based on the studies of Clawson, Bell, and Hartzell.

Age and Sex Incidence. Prognosis. Chronic valvular disease is a condition of the fourth and fifth decades of life. Both the sex of the patient and the valves involved influence prognosis.

The following generalities are apparent: disease of the mitral valve is more frequent in women and of the aortic valve in men, and women with all types of chronic valvular disease live longer than men with valvular disease.

Causal Factors. It is generally assumed that most chronic endocarditis is the end stage of the effect of rheumatic fever on the heart. This assumption rests on the high incidence of rheumatic fever in the history of those with chronic valvular disease, the chronologic sequence of events in selected patients, and the association with other lesions also probably caused by rheumatic fever. The technique of this type of analysis is well shown in the fig-

hearts show a slight thickening of the valves and adhesions between the leaflets. In southern California Hall and Anderson report that 90 per cent of all adult hearts show this lesion. In St. Louis and in Cleveland the incidence is 40 to 60 per cent. Whether or not rheumatic fever is the cause must remain for future determination. If it is, it means that rheumatic fever is a widespread disease affecting most of the population.

TABLE 39. EVIDENCES OF RHEUMATIC FEVER IN CHRONIC VALVULAR DISEASE

Item	All Types (Per Cent)	Aortic Stenosis (Per Cent)
History of rheumatic fever.....	41	35 —48.4
Pericarditis.....	18—66.6	16 —36.8
Lesion of another valve.....	—	44.5—38.7
Aschoff's bodies.....	13—58.3	13 —47.3

ures of Clawson, Noble, and Lufkin (first figures in table), and those of Hall and Ichioka (second figures in table) in their studies of calcified nodular aortic stenosis.

These figures leave a good deal to be desired, but are the best evidence available until such time as a pathognomonic lesion of healed rheumatic fever is established.

Clinicopathologic Correlation. Clinical manifestations of chronic valvular disease depend on many factors, and there is not space in this book to discuss all of them. The more important bearing on the clinicopathologic correlation are: disturbances in the flow of blood causing adventitious sounds, hypertrophy and dilatation of the heart resulting in alterations in the size and shape as determined by percussion or by radiographic examination, escape of emboli from the thrombi in the cavities of the heart with the usual embolic manifestations, and failure of the myocardium to overcome the valvular incompetence or stenosis and consequent cardiac decompensation.

Relative Insufficiency. A murmur, usually systolic, and heard best over the mitral area, is present in many patients who at autopsy show no deforming lesion of the valves. Some have been attributed to relative insufficiency resulting from dilatation of the valvular rings. Anatomic study of the size of the valves in relation to the size of the orifice gives no support for this concept (Gross and Moore).

Chronic Nondeforming Endocarditis. Many

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LXXXVI

Arteriosclerosis: Complications and Sequelae

In studying the syndrome variously known by clinicians as "arteriosclerotic heart disease," "cardiovascular-renal disease," "hypertensive heart disease," or "degenerative heart disease," the pathologist must consider both the anatomic lesions of the blood vessels and the effects on certain viscera of alterations in the quantity and pressure of the blood.

The anatomic lesions in the vessels fall into four classes: lipoidosis, intimal arteriosclerosis, medial arteriosclerosis, and arteriolosclerosis. Because of the intimate relations of arteriolosclerosis to disease of the kidney it will be discussed in the succeeding chapter (p. 737). The other three and their effects will be discussed in this chapter.

Selection of Terms. Many terms have been used to designate chronic, noninflammatory lesions of blood vessels, notably "atheroma," "atherosclerosis," and "arteriosclerosis." The first two of these give undue prominence to the fatty change, while the latter is completely noncommittal as to cause and pathogenesis and therefore the most desirable.

Lipoidosis of the Arteries

Pathologic Anatomy. In the intima of the artery are small, bright yellow, slightly elevated, nonindurated, round foci or streaks. The sites of predilection are the posterior wall of the aorta between and about the orifices of the intercostal arteries, and the first few centimeters of the ascending aorta. In the plaques are numerous droplets of fat, extracellular and in macrophages. The adjacent elastica is slightly frayed, but there is no change in the underlying media. In association with some deposits there is slight proliferation of fibroblasts.

Incidence. Minimal lipoidosis is observed during the first decade of life, and by the

age of ten is present to some extent in almost every aorta, and at times in the primary branches of the aorta, especially the coronary arteries.

Significance. It is highly probable that the deposition of fat in lipoidosis is reversible, and that the plaques come and go throughout childhood, but that in older persons lipoidosis may progress to true arteriosclerosis. The reasons for this belief are that transitional lesions are observed, and that lipoidosis and arteriosclerosis occur in the same locations.

Intimal Arteriosclerosis

Pathologic Anatomy. It is not possible to describe arteriosclerosis chronologically, from the earliest lesions to the oldest, because there is as yet no general agreement on pathogenesis. The alternative is a separate description of each of the essential changes.

Deposit of Fat. In small plaques the change is essentially that of lipoidosis. Droplets of fat are in all parts of the intima, together with proliferation of fibroblasts. In larger lesions not only are droplets of fat seen, but also fusiform crystals of cholesterol and cholesterol esters. The associated fibrosis in the luminal layers of the plaque covers the yellow color, but at the periphery and on the cut section the typical yellow, soft mass is discernible.

Fibrosis. Even in small plaques there is proliferation of fibroblasts in and about the deposits of fat. In larger lesions the connective tissue is most conspicuous just beneath the endothelium and is responsible for the pearly gray elevations seen macroscopically. In many, the collagen undergoes hyalinization and at times necrosis to fuse with the liquefied lipid.

Hemorrhage. In both small and large lesions, and also in relatively normal intima,

there are small recent and healed foci of hemorrhage.

Fraying of the Elastica. At the edge of all plaques the elastic fibers of the intima are frayed and broken. As subendothelial fibrosis appears, an irregular, imperfect, new elastic lumina may be deposited.

Ulceration and Thrombosis. In larger plaques the hyalinized fibrous tissue over a softened mass of lipid may undergo necrosis and expose the deeper structures as an ulcer, which is quickly covered by a fine fibrinous thrombus. Rarely, the thrombus grows to occlude the vessels (Greenfield).

Calcification. In many plaques there are spherical or flat foci of calcification, apparently beginning about the lipid and the hyalinized connective tissue.

Changes in the Media. Small plaques do not involve the media, but larger ones may extend into and gradually destroy the media. In the coronary arteries there is atrophy of the media beneath a plaque, but no direct extension. The adjacent tissue is fibrotic, and there is a perivascular lymphocytic infiltration in the media and adventitia, at times confusing in the differential diagnosis from syphilis.

Dilatation. All vessels with any significant arteriosclerosis are less elastic than normal, and dilated and lengthened.

Location of Lesions. Although plaques may form in any part of the arterial wall, there are more about the orifices of the branches of the parent vessel and in the first few centimeters of the branches.

Pathogenesis. There are three prominent concepts of the initial lesion of arteriosclerosis: that there is a physiochemical change in the collagen of the intima (Aschoff), that the fat in the blood passes through the endothelium and is deposited in the subintimal tissues (Leary), and that there is a small hemorrhage in the intima, the red blood cells of which break down to liberate fat (Winternitz, Thomas, and Le Compte). It is not possible now to decide which of these postulations is cause and which is effect.

Incidence. In routine autopsies the lesions of arteriosclerosis are first observed in those of the third decade, and progressively increase in frequency and severity with increasing age. Advanced arteriosclerosis is reported in 20

to 30 per cent of all persons over forty years of age, in all parts of the world and in all races.



Fig. 350. Arteriosclerosis of aorta. Note elevated plaques, especially about the orifices of branches, and ulceration in the abdominal aorta. (MacCallum.)

Most statistics indicate a slight preponderance in men (Anitschkow).

Causal Factors. Arteriosclerosis is prob-

ably a disease of multiple causes, no one of which is operative alone. The factors so far established on the basis of objective evidence are discussed in succeeding paragraphs.

Disturbance of Fat Metabolism. Negative evidence on this point includes the occurrence of arteriosclerosis without regard for the state of nutrition, and the usually normal total serum fat and cholesterol in patients with arteriosclerosis. Positive facts are the claimed greater incidence of arteriosclerosis, particularly of the coronary arteries, in diabetes; the greater incidence of arteriosclerosis in those

Direct Trauma to the Vessels. BY NORMAL FUNCTION. With each systole of the heart the arterial tree is slightly elongated. Each vessel is least elastic and least movable at the origin of the branches. Hence numerous points are subjected to minute trauma seventy-two times a minute for many years. The frequent location of plaques about the orifices and in the first few centimeters of the branches supports the concept that physiologic trauma is an important localizing, if not causal, factor.

BY HYPERTENSION. Arteriosclerosis is more common in those with hypertension. It might

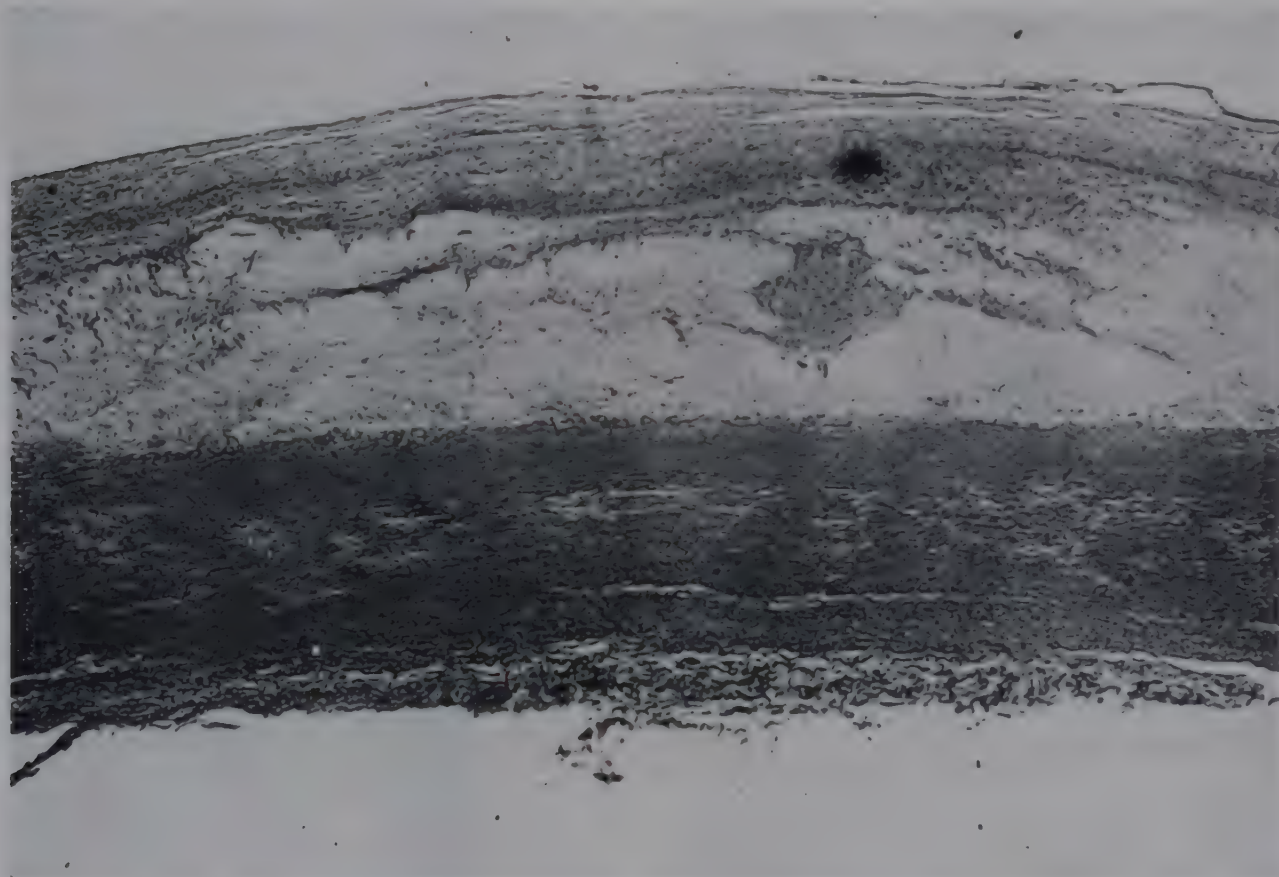


Fig. 351. Arteriosclerotic plaque of intima of aorta.

who also have gallstones; the parallelism between arteriosclerosis and the storage of lipid in the adrenal; and the prominent part played by fat in the pathologic change of arteriosclerosis (Hirsch and Weinhouse).

Endocrine Glands. Arteriosclerosis occurs with equal frequency in regions where hyperthyroidism is endemic and in regions where it is rare. The claimed association of focal hyperplasia of the adrenal cortex and the established relation of basophilism to arteriosclerosis and hypertension are not pertinent to the problem of arteriosclerosis.

Toxic Substances. There is no real evidence that alcohol or nicotine is a cause of arteriosclerosis. Similarly, other substances such as lead and morphine have no proved relation.

be argued that this is nothing more than the association of two closely related conditions. However, the known association of arteriosclerosis of the pulmonary artery with all conditions which increase pulmonary blood pressure—mitral lesions, fibrosis of the lung, emphysema—is strong presumptive evidence for a causal relation.

BY MOVEMENT. By and large, arteriosclerosis is more apparent in the right arm and leg of right-handed persons, in the legs of those whose occupation requires excessive walking, and in the one leg used in some mechanical operations such as driving a sewing machine for many years.

BY CONCOMITANT DISEASE OF THE VESSELS. Arteriosclerosis of the aorta, if present, is far more severe in those with syphilitic aorti-

tis. In fact, Warthin observed advanced arteriosclerosis twenty-five times as frequently in persons with syphilis as in those free of syphilis.

Inflammation. Many have noted the high incidence of arteriosclerosis in those who have had infectious disease such as scarlet fever, pneumonia, etc. (MacCallum). There is however no proof of the causal relation, except in rheumatic fever (Karsner and Bayless).

Medial Arteriosclerosis

The muscular arteries of the extremities show a distinctive type of arteriosclerosis. The incidence of intimal arteriosclerosis and medial arteriosclerosis is not always correlated, and the pathologic changes are so different that it seems desirable to discuss them separately.

Pathologic Anatomy. The artery is slightly dilated and irregularly firm. The firmness consists of irregular, incomplete, circular rings of calcification. The calcification is in the media. The smallest lesions are encrustations of calcium on the elastic fibers. With increase in size there are fusion and the formation of larger plaques. In some there is conversion of the calcified masses to osteoid tissue and bone with bone marrow. The intima between the rings of calcium is thickened by proliferation of connective tissue. There is some evidence that fatty degeneration precedes the deposit of calcium. In general, the diameter of the lumen is not decreased.

Calcification of the Aortic Media. In the aortas of many older persons there is minimal calcification in the media, consisting of encrustation on the elastic fibers of the middle third. There is no proved relation to other types of arteriosclerosis or to any other disease.

Nonuse Sclerosis. In the ovaries and uterus of the postmenopausal woman there is thickening of the walls of the vessels, by proliferation of the subintimal tissues and the formation of smaller complete vessels within the former lumen. There is at the same time hyalinization of the media, and not infrequently calcification. A somewhat similar lesion is found in larger vessels which are no longer carrying the normal amount of blood, such as in the splenic artery after splenectomy, and in a renal artery after nephrectomy.

Complications and Sequelae of Arteriosclerosis

Although arteriosclerosis may and does at times affect every major artery in the body, there are certain ones which are more fre-

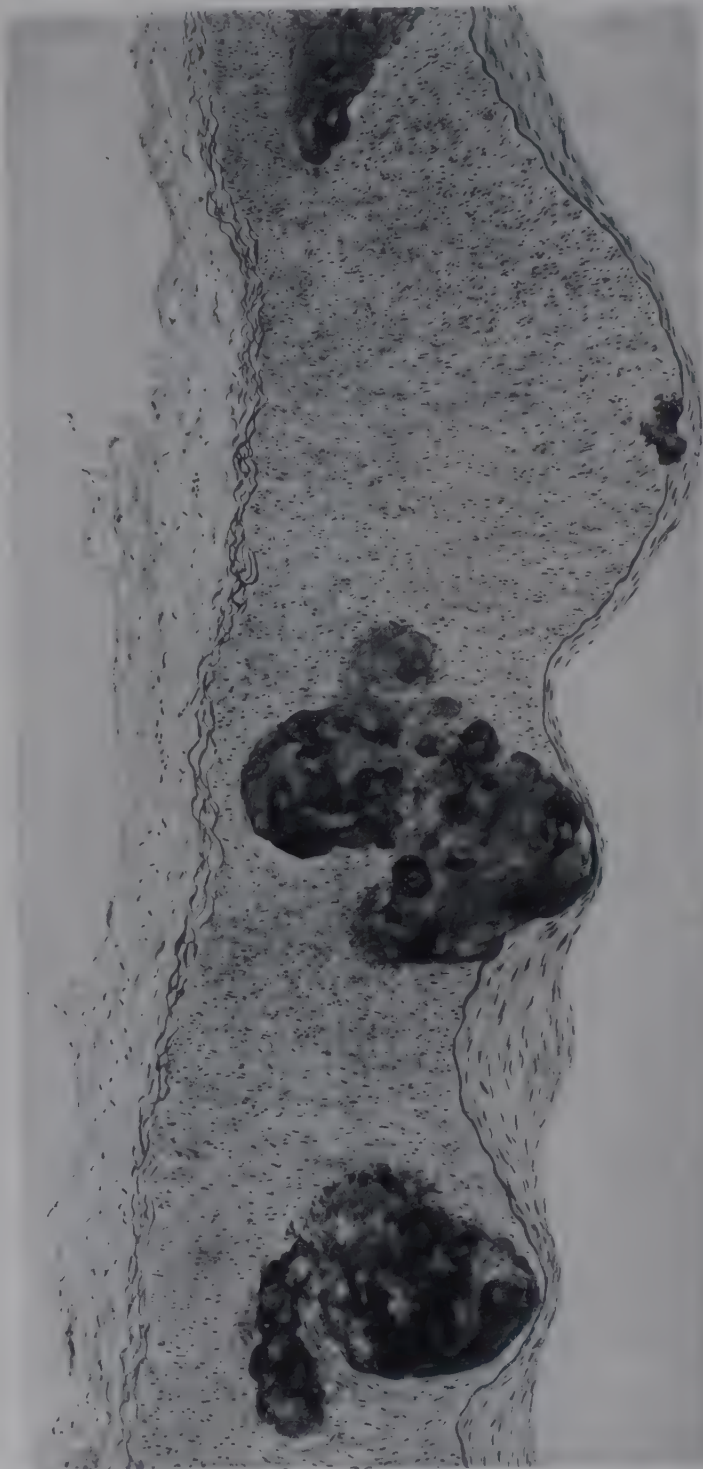


Fig. 352. Medial sclerosis of Mönckeberg in a femoral artery in longitudinal section. The calcified rings are seen in cross-section. (MacCallum.)

quently involved and from which signs and symptoms are common. These are the coronary arteries, the cerebral arteries, and the arteries to the extremities.

Arteriosclerosis acts in a number of ways: first, by partially occluding the lumen and thus decreasing the minute volume of flow to a part with atrophy and fibrosis of that part; second, by weakening the wall so that either

an aneurysm forms or there is sudden rupture; third, by both partial occlusion and erosion of the intimal surface so that an occluding thrombus forms and leads to an infarct of the supplied part.

Coronary Arteriosclerosis—Cardiac Infarct

Cardiac failure with or without infarction is the immediate cause of death in about 60 per cent of patients with hypertension.

Coronary Arteriosclerosis. The pathologic anatomy of arteriosclerosis of the coronary arteries is essentially the same as that of arteriosclerosis of the aorta.

Intercoronary Anastomoses. The major branches of the coronary arteries in a normal

work of the heart: effort, infection, and hypertension. Of all sudden and unexpected deaths, disease of the coronary artery is responsible for about 40 per cent (Hamman).

Focal Fibrosis of the Myocardium. Many hearts with slight to moderate arteriosclerosis of the coronary arteries show numerous small foci of fibrosis throughout the myocardium. These are more prominent in perivascular tissue and cause a separation of the muscle fibers. There are occasionally a few lymphocytes, but the older designation of "chronic interstitial myocarditis" is not correct.

Occlusion of the Coronary Arteries. Many different lesions may bring about complete occlusion of one or more branches of the coronary arteries. The commonest is a thrombus formed over an arteriosclerotic plaque.

TABLE 40. DISTRIBUTION OF OCCLUSION OF CORONARY ARTERIES

Artery	Occlusions Found at Given Distances from the Coronary Orifices			Total	Per Cent
	0-3 Cm.	4-6 Cm.	6-10 Cm.		
Left descending.....	29	15	6	50	40
Left circumflex.....	19	9	5	33	26
Right.....	20	10	12	42	34
Totals.....	68	34	23	125	100

heart show few anastomoses with a diameter of over 40 microns. In contrast, hearts with significant narrowing of the coronary arteries have numerous communications measuring 40 to 120 microns in diameter. The development of these anastomoses is directly related to coronary arteriosclerosis, since they are not present in the hearts of older persons without coronary disease.

Unexpected Death in Coronary Arteriosclerosis. The medical examiner sees a fairly large number of persons in whom unexpected death apparently resulted from sudden cardiac failure. The heart is usually enlarged, and there is slight to moderate arteriosclerosis, but no demonstrable occlusion of an artery and no infarct of the myocardium. It is assumed that the sudden anoxemia is the result of factors other than anatomic narrowing of the vessels. Among these are factors which decrease the nutritional supply to the heart: lowered blood pressure, anemia, and passive congestion; and factors which increase the

Less frequent causes are hemorrhage into the wall (Wartman), embolism (Garvin and Work), and discharge of the contents of an arteriosclerotic plaque into the circulation (Leary).

Location of Occlusion. In 125 examples of occlusion of the coronary arteries studied by Schlesinger and Zoll, the distribution was as shown in Table 40.

Infarct of the Heart. Pathologic Anatomy. The pathologic changes in the heart in infarction vary with the time of survival of the patient after the moment a region of the myocardium is deprived of adequate blood supply.

WITH DEATH WITHIN A FEW HOURS. There is no demonstrable change in the myocardium. The fibers are well preserved. After from three to six hours there is beginning focal hyperemia, and in four or ten hours there are slight loss of striation, hemorrhage, infiltration of leukocytes, changes in the nuclei, and interstitial edema.

WITH DEATH IN A FEW DAYS. After two to

fifteen days the picture usually associated with a cardiac infarct is seen. The focal region of the myocardium is yellow, soft, and friable. The outline is fairly sharp and the surrounding tissue red. In about half of the cases there are changes in the endocardium and pericardium. On the endocardial surface of the ventricle is a laminated thrombus, and over the region of the infarct the pericardium is covered by a fine fibrinous exudate.

WITH DEATH IN A FEW WEEKS. After two or three weeks there is beginning organiza-

tion of the infarct. The organized part appears on a cut surface as a bluish gray, slightly depressed focus. The necrotic muscle is in part removed, and the granulation tissue is edematous and richly vascularized. Many phagocytes containing hemosiderin are seen. In the adjacent living muscle there is attempted regeneration. The fibers have bulbous ends and are multinucleated. The endocardial thrombus and the fibrinous pericarditis show a corresponding degree of organization.

Pathogenesis. Infarcts are occasionally seen without demonstrable occlusion of the coronary arteries (Gross and Sternberg), and the region of the infarct does not always correspond to the distribution of the occluded vessel (Blumgart, Schlesinger, and Davis). Hence there must be many other factors which influence the origin and site of an in-

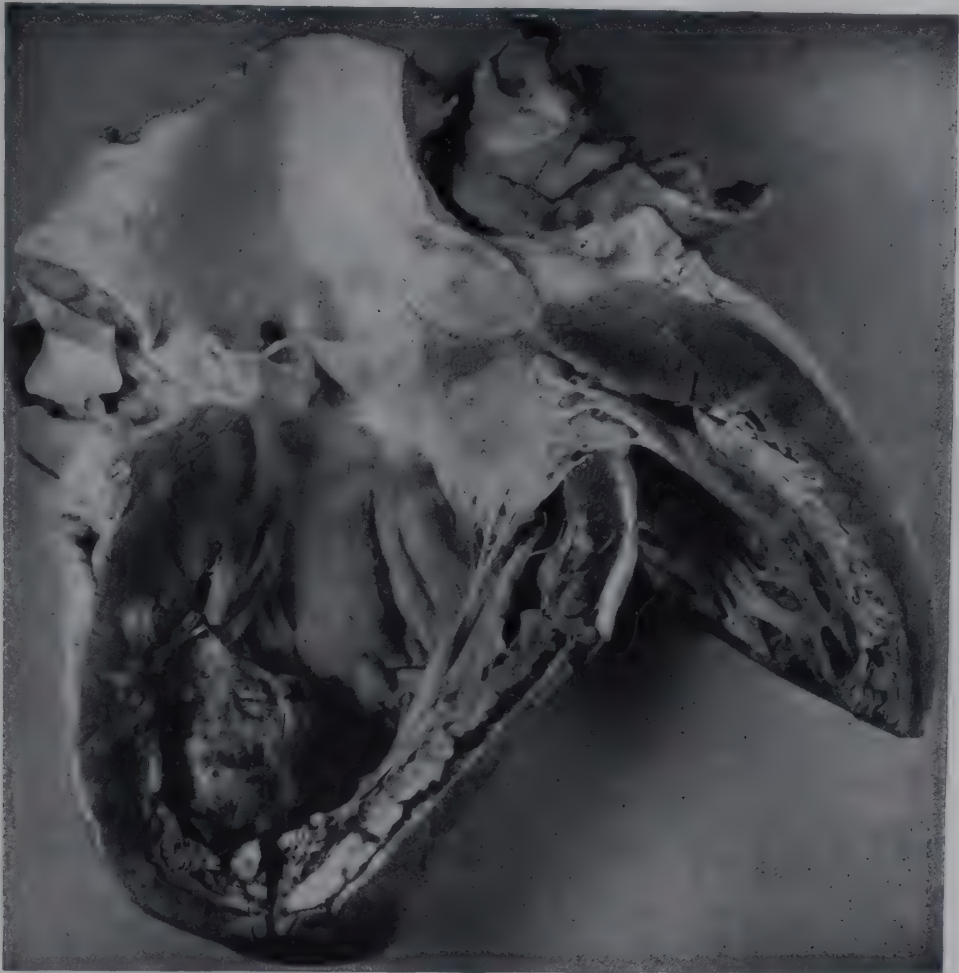


Fig. 353. Infarct of wall of left ventricle. (MacCallum.)

tion of the infarct. The organized part appears on a cut surface as a bluish gray, slightly depressed focus. The necrotic muscle is in part removed, and the granulation tissue is edematous and richly vascularized. Many phagocytes containing hemosiderin are seen. In the adjacent living muscle there is attempted regeneration. The fibers have bulbous ends and are multinucleated. The endocardial thrombus and the fibrinous pericarditis show a corresponding degree of organization.

WITH DEATH AFTER MANY MONTHS. Infarcts of average size are completely replaced by fibrous tissue in six to eight months. The pericardium over the region is thickened or is adherent. The endocardial thrombus has been completely organized, and the endocardium is

thick, gray, and opaque. The myocardial wall is thin, and the greater part is an interlacing mass of dense connective tissue, with only a few isolated strands of muscle.

Complications and Sequelae. Aside from the pericarditis and the endocardial thrombus already mentioned, the most serious complications and sequelae of a cardiac infarct are rupture of the heart, aneurysm of the heart, and systemic embolism.

Rupture of the heart. The soft necrotic myocardium may give way to the force of the intraventricular pressure. Blood pours out into the pericardial sac and sudden death ensues. The site of rupture in four of five is the left ven-

tricle (Krumhaar and Crowell). Rupture through the interventricular septum results in characteristic signs (Fowler and Failey).

ANEURYSM OF THE HEART. With the healing of an infarct the wall may be so weakened that it is unable to withstand the intraventricular pressure, and gradually dilates to form an aneurysmal sac extending outward from the surface of the heart. The sac is adherent to the pericardium by dense fibrous adhesions, and is lined by a thick, white opaque endocardium.

SYSTEMIC EMBOLISM. The thrombi formed in the ventricles over an infarct serve as a source of emboli to the spleen, kidneys, brain, intestines, and extremities. The embolic manifestations are usually seen after the eighth to the tenth day, and may cause death (Garvin).

CALCIFICATION OF MYOCARDIUM. Under circumstances in which there is delayed resorption of necrotic muscle fibers, produced by ischemia or infection, calcification may ensue (Gore and Arons).

Angina Pectoris. Angina pectoris is a symptom complex characterized by paroxysmal pain, usually pectoral, provoked by an increase of the demands on the heart, and relieved by a diminution of the work of the heart. Sudden death is a likely termination (Keefer and Resnik). The known occurrence of the syndrome in coronary arteriosclerosis, aortic insufficiency, arteriovenous fistulas, pericarditis, mitral stenosis, and anemia—all conditions associated with decreased coronary blood flow—indicates that the cause is anoxemia of the myocardium (Feil and Beck).

Incidence. Coronary arteriosclerosis and myocardial infarct are lesions of increasing age. Figures for the Army in World War II show an incidence of 0.1 per 100,000 at ages 18 to 19, and of 12.7 at ages 35 to 39 (Yater, Traum, Brown, Fitzgerald, Geisler, and Wilcox). Thereafter the incidence rises sharply. It is slightly more common in men in a ratio of 6:4.

Clinicopathologic Correlation. The onset of symptoms with an infarct is sudden. The clinical manifestations are directly related to the pathologic changes (Blumgart, Schlesinger, and Davis).

Pain is not caused by occlusion of the artery, but is the result of the accumulation of metabolites in a myocardium with inadequate circulation, or caused by the presence of the

products of necrosis of tissue. The peripheral distribution corresponds in general to the concept of referred pain.

The loss of a large part of the left ventricular muscle is the basis for the syndrome similar to that of peripheral circulatory failure or of shock. The heart is no longer able to maintain an adequate minute-volume output. The disproportion between the capacities of the right and left ventricles induces acute pulmonary hyperemia and edema.

The late elevation of temperature and increase in leukocyte count are the result either of the absorption of dead tissue or of the deposition of a thrombus in the ventricles. The pericarditis is fibrinous, with minimal fluid, so a friction rub is usually heard.

Cerebral Hemorrhage—Apoplexy

Contrary to common belief, cerebral hemorrhage, thrombosis, and embolism are not common causes of unexpected, sudden death. In one analysis of 853 cases of sudden death, disease of the coronary arteries was the cause in 40 per cent, aneurysm of the aorta in 12 per cent, valvular disease of the heart in 12 per cent, and cerebral hemorrhage in only 8 per cent (Hamman).

Pathologic Anatomy. In the well-developed large cerebral hemorrhage the brain is edematous and the convolutions flattened. The meninges may be slightly thickened and the larger arteries coursing in the subarachnoid space are thickened and firm. One hemisphere is usually larger and softer than the other. At the base, blood may be in the cisterns, and on slight pressure can be seen issuing from the foramina in the fourth ventricle. The usual site of hemorrhage is in the basal ganglia and internal capsule. The tissue is torn apart, and a cavity filled with liquid blood forms. The walls of the cavity are composed of friable, hemorrhagic tissue. In some, the cavity ruptures into one of the lateral ventricles, and the entire ventricular system is filled with liquid or clotted blood. Frequently, there are small, streaklike hemorrhages in the cerebral peduncles and in the pons.

Pathogenesis. There is no agreement on the mechanism of cerebral hemorrhage. One theory postulates that arteriosclerosis and thrombosis of small vessels cause foci of encephalomalacia. The softening weakens the

pressure on the walls of the larger vessels, which then rupture. Another theory assumes that primary arteriolar spasm takes place and later the capillaries dilate. There is diapedesis, and as the spasm continues there are necrosis and rupture of a larger vessel. Miliary aneurysms have been suggested as the mechanism, but they are only occasionally demonstrable; and rupture of an arteriosclerotic plaque is plausible as a mechanism, but cannot be proved (Globus; Bouman).

Atrophy of the Brain in Arteriosclerosis. In many older patients with arteriosclerosis, but without focal lesions of hemorrhage or encephalomalacia, the brain is smaller than normal, and the convolutions, especially in the frontal and parietal regions, are decreased in size. The sulci are correspondingly widened, and there is an increase of fluid in these regions. The lateral ventricles are dilated, and the normally sharp-pointed extremities of the ventricular horns are rounded. The leptomen-

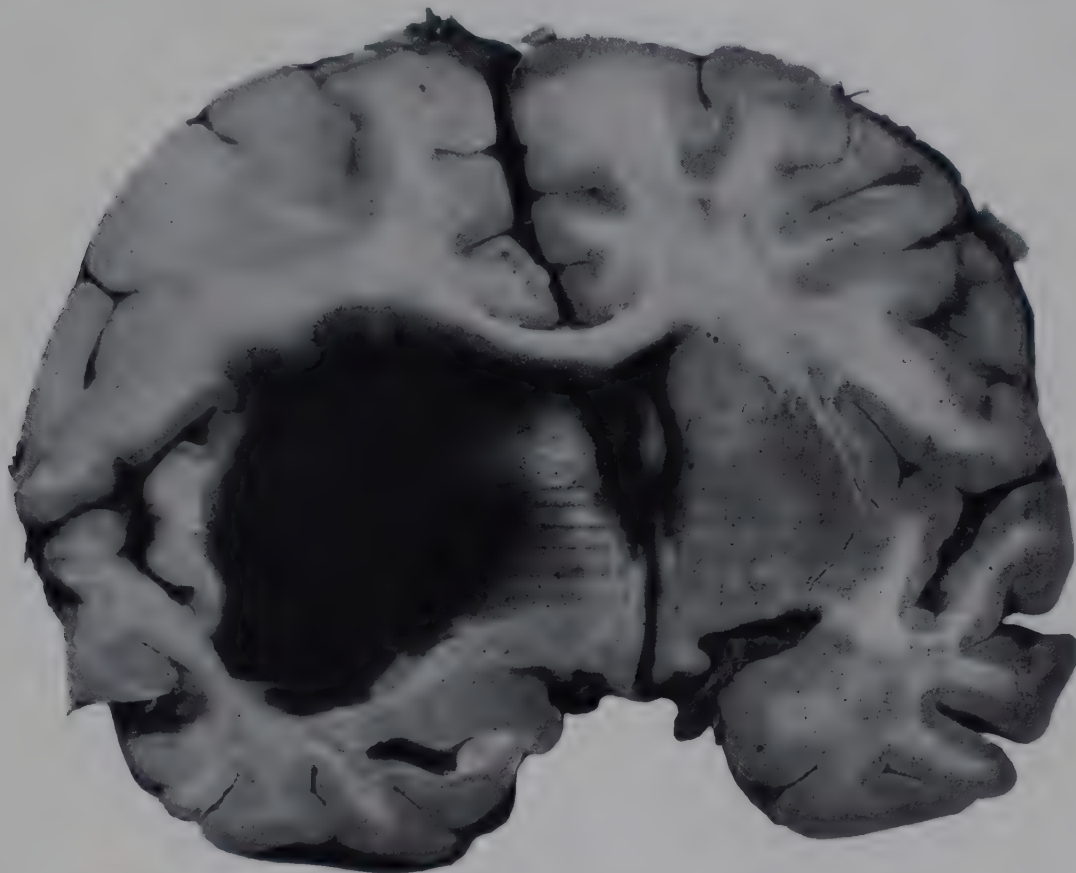


Fig. 354. Cerebral hemorrhage with rupture into ventricles.

Cerebral Thrombosis and Embolism. Occlusion of a cerebral vessel by a thrombus is usually based on severe arteriosclerosis, while cerebral embolism is a complication of acute endocarditis, of chronic valvular disease with thrombi in the atria, and of cardiac infarction with intraventricular thrombi. It occurs most frequently in the middle cerebral artery, and hence the roughly pyramidal region of softened cerebral substance is in the parietal and posterior frontal lobes. The focus of encephalomalacia is at first soft and hemorrhagic. Gradually, there are liquefaction and the formation of a definite wall. The final stage is a cyst filled with clear, limpid fluid, and lined by a brown membrane composed of fibrous tissue and glia. There may be one large cyst or numerous small cysts, the latter more frequently observed in the region of the basal ganglia.

inges are slightly thickened and opaque (see discussion of senile and presenile atrophy of the brain, p. 943).

Clinicopathologic Correlation. Cerebral hemorrhage and encephalomalacia are seen in patients over sixty or seventy years of age. Usually there are premonitory signs of slight cerebral disturbance, attributed to small foci of encephalomalacia and to small initial hemorrhages. With rupture of the large vessel there is loss of consciousness, chiefly on the basis of a sudden increase of intracerebral pressure. With resorption of fluid and adjustment of the cerebral pressure, consciousness is usually regained after a few hours or days. Localizing signs such as monoplegia, hemiplegia, or quadriplegia serve to indicate the location of the hemorrhage. Sudden death during this period is usually the result of rupture of the hemorrhage into the ventricular system, with

the consequent increase of pressure within the fourth ventricle and dysfunction of the cardiac and respiratory centers in that part of the brain stem. In the usual hemorrhage, with tearing of the internal capsule on one side, there is permanent residual hemiplegia of varying degree. Patients with cerebral hemorrhage rarely die in less than five minutes after the onset of symptoms, and the average survival in one large series was 81.3 days.

Vascular Disturbances of the Extremities

Arteriosclerotic Gangrene. *Pathologic Anatomy.* In the usual case of arteriosclerosis of the arteries of the extremities and gangrene the arteries are the seat of both intimal and medial sclerosis. The lumen is filled with a recent or partially organized thrombus, most evident in the popliteal artery, with exten-

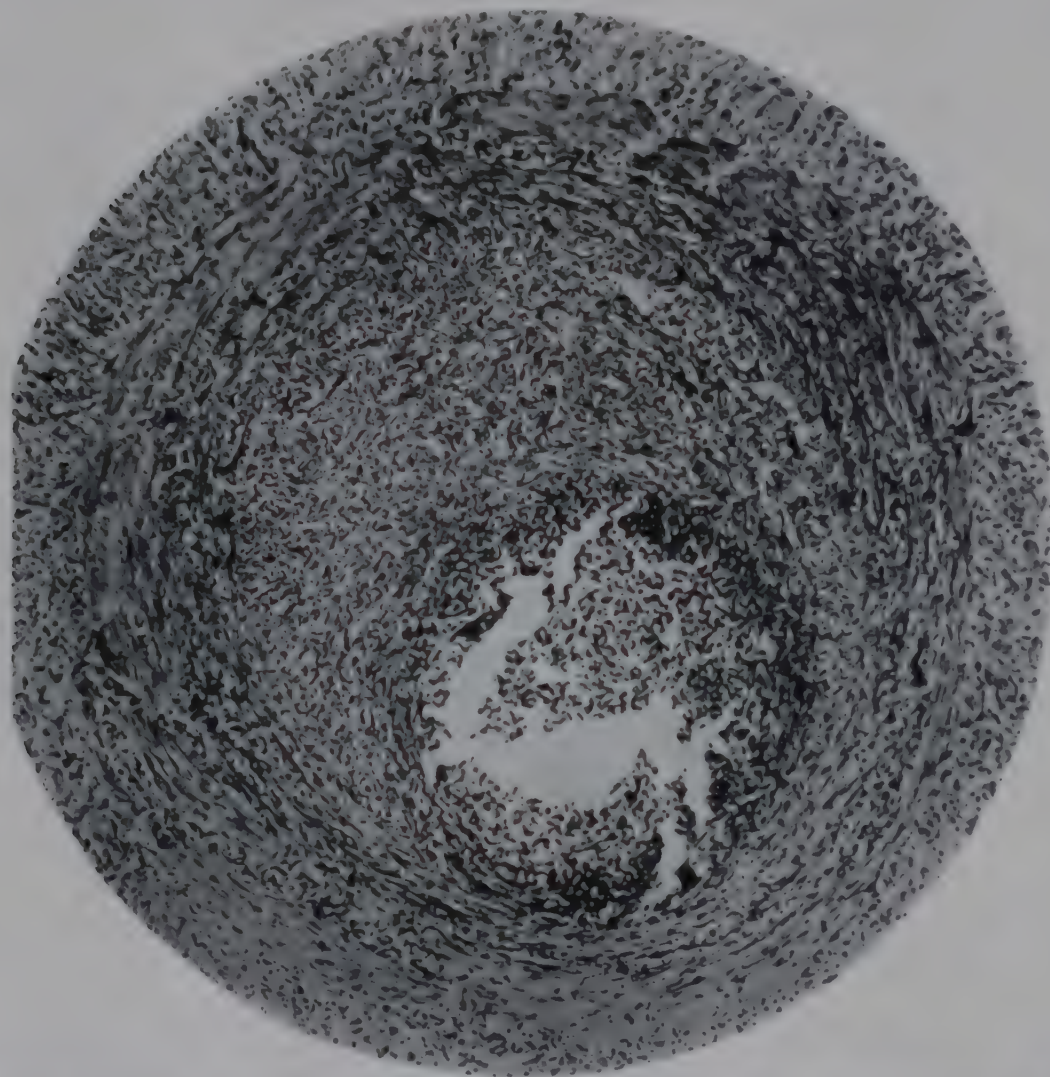


Fig. 355. Thrombo-angiitis obliterans. (Buerger: *The Circulatory Disturbances of the Extremities*.)

Death within a few days is usually seen after hemorrhage into the brain stem, and occurs in patients in early adult life (Newbill).

Other Types of Cerebral Hemorrhage. Less common types of cerebral hemorrhage include hemorrhage into a tumor (Schultz), rupture of varices, hemorrhage during labor or the puerperium, without evident disease of the cerebral vessels (Moskowitz and Schneider), and hemorrhage in scurvy and in thrombocytopenia. Intracranial hemorrhage not into the brain substance is discussed under other titles: "Epidural Hemorrhage," p. 480; "Subdural Hematoma," p. 481; and "Aneurysm of the Cerebral Arteries," p. 769.

sion into the femoral and posterior tibial arteries.

Dry gangrene begins as a paleness and coldness of the part. Soon there are brownish red discoloration and dryness. Finally, the region is converted into a small, hard, black mass. Rarely, there is wet gangrene, with edema of the tissues and bleb formation in the skin. At the line of junction with normal tissue, which is sharp, there is a zone of inflammation with granulation tissue.

Incidence. Arteriosclerotic gangrene is seen after fifty, and is commoner in men than women. Some claim that gangrene has a higher incidence in diabetics than in others.

Thrombo-angiitis Obliterans (Buerger's Disease). *Pathologic Anatomy.* The earliest lesion is an acute inflammation of all layers of the walls of the arteries and veins and occlusion of the lumens by thrombi. The wall is infiltrated with leukocytes, and in the thrombi focal accumulations of leukocytes take on the appearance of abscesses. In the wall there are giant cells. With healing, the thrombus is organized. The wall is fibrotic, and the artery, vein, and nerves become densely adherent to one another. There is no demonstrable elastic tissue in the organized thrombus, and throughout all parts there is a slight infiltration with lymphocytes.

Lesions are commonest in the peripheral parts of the vessels of the leg, and less common in the arms, but the entire vascular system of an extremity may be sectionally or continuously involved. Most examples are bilateral (Buerger). Similar lesions have been described in the visceral vessels.

The disease has been described in all races. The average age of onset is in the early thirties. The cause is unknown.

Raynaud's Disease. This is a disease affecting the peripheral parts of the body—extremities, nose, and ears. In the initial stage there is local syncope or asphyxia. In the former the peripheral part is cold and pale, while the latter is recognized by a change to a bluish red color and swelling of the tissues. A second stage is characterized by trophic disturbances—vesicles and ulcers of the skin and atrophy of bone, even to the disappearance of the terminal phalanges. In the final stage there is gangrene, rarely involving a large segment. At all stages the lesions are typically symmetrical. The cause is unknown. The peak incidence is in the third decade. The sex ratio of women to men is 7:3 (Hyndman and Wolkin).

A similar clinical picture may be caused by a wide variety of lesions which induce hypoxia. It should be designated Raynaud's syndrome.

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LXXXVII

Bright's Disease—Renal Insufficiency

In 1827, 1831, and 1836, Richard Bright of London recorded for posterity his observations on the clinicopathologic correlation of diseases of the kidney. No better introduction to this subject could be given than to quote the description given by Bright (Guy's Hospital Reports, Vol. I, pp. 339–341):

A child, or an adult, is affected with scarlatina, or some other acute disease; or had indulged in the intemperate use of ardent spirits for a series of months or years; he is exposed to some casual cause or habitual source of suppressed perspiration: he finds the secretion of his urine greatly increased, or he discovers that it is tinged with blood; or, without having made any such observation, he awakes in the morning with his face swollen, or his ankles puffy, or his hands oedematous. If he happen, in this condition, to fall under the care of a practitioner who suspects the nature of his disease, it is found that already his urine contains a notable quantity of albumin. His pulse is full and hard, his skin dry, he has often headache, and sometimes a sense of pain or weight across the loins. Under treatment more or less active, or sometimes without any treatment, the more obvious and distressing of these symptoms disappear; the swelling, whether casual or constant, is no longer observed; the urine ceases to evince any admixture of red particles; and, according to the degree of importance which has been attached to these symptoms, they are gradually lost sight of, or are absolutely forgotten. Nevertheless, from time to time the countenance becomes bloated; the skin is dry; headaches occur with unusual frequency; or the calls to micturition disturb the night's repose. After a time, the healthy color of the countenance fades; a sense of weakness or pain in the loins increases; headaches, often accompanied by vomiting, add greatly to the general want of comfort; and a sense of lassitude, of weariness, and of depression, gradually steal over the bodily and mental frame. Again the assistance of medicine is sought. If the nature of the disease is suspected, the urine is carefully tested; and found, in almost every trial, to contain albumin, while the quantity of urea is gradually diminishing. If, in the attempt to give relief to the oppression of the system, blood is drawn, it is often buffed, or the serum is milky and opaque; and nice analysis will frequently detect a great deficiency of albumin, and sometimes manifest indications of the presence of urea. If the disease is not suspected,

the liver, the stomach, or the brain divide the care of the practitioner, sometimes drawing him away altogether from the more important seat of disease. The swelling increases and decreases; the mind grows cheerful or is sad; the secretions of the kidney or the skin are augmented or diminished, sometimes in alternate ratio, sometimes without apparent relation. Again the patient is restored to tolerable health; again he enters on his active duties: Or he is, perhaps, less fortunate;—the swelling increases, the urine becomes scanty, the powers of life seem to yield, the lungs be-

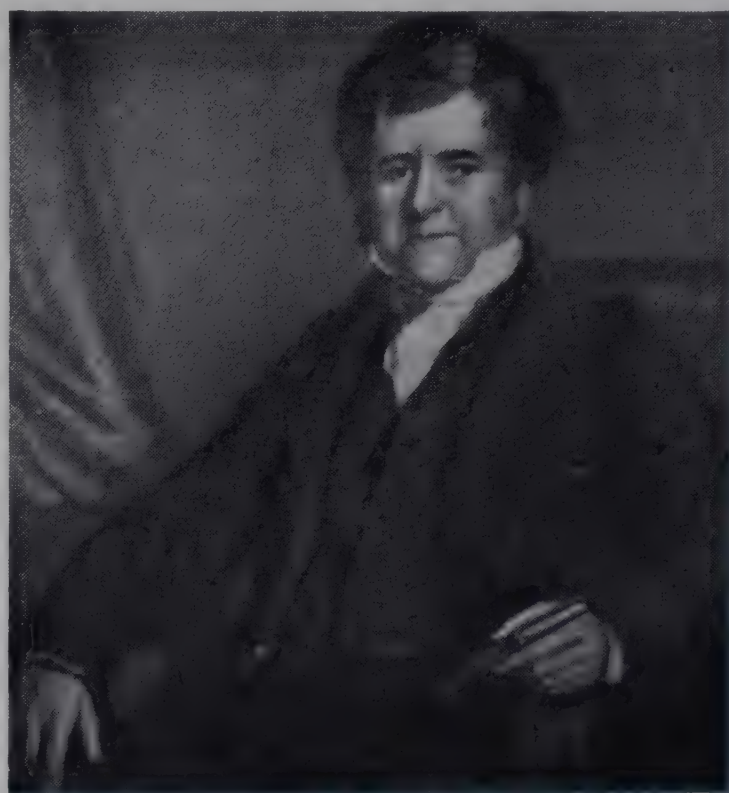


Fig. 356. Richard Bright, 1798–1858. (Garrison.)

come oedematous and, in a state of asphyxia or coma, he sinks into the grave; or a sudden effusion of serum into the glottis closes the passages of the air, and brings on a more sudden dissolution. Should he, however, have resumed the avocations of life, he is usually subject to constant recurrences of his symptoms; or again, almost dismissing the recollection of his ailment, he is suddenly seized with an acute attack of pericarditis, or with a still more acute attack of peritonitis, which, without any renewed warning, deprives him, in eight and forty hours, of his life. Should he escape this danger likewise, other perils await him; his headaches have been observed to become more frequent; his stomach more deranged; his vision in-

distinct; his hearing depraved; he is suddenly seized with a convulsive fit, and becomes blind. He struggles through the attack; but again and again it returns; and before a day or week has elapsed, worn out by convulsions, or overwhelmed by coma, the painful history of his disease is closed.*

Classification of Bright's Disease

Careful study of the anatomic descriptions given by Bright reveals that he was dealing with many different lesions of the kidney. During the century which has elapsed since that time, many classifications have been proposed. The following classification is essentially that proposed by Volhard and Fahr, and by Bell:

- I. Nephrosis (degenerative Bright's disease)
 1. Acute
 2. Chronic
 - (a) Lipid
 - (b) Amyloid (p. 14)
- II. Glomerulonephritis (hemorrhagic Bright's disease)
 1. Focal (p. 718)
 2. Diffuse
 - (a) Acute
 - (b) Subacute
 - (c) Chronic
- III. Nephrosclerosis (arteriosclerotic Bright's disease)
 1. Arterial
 2. Arteriolar
 - (a) Slowly developing (benign)
 - (b) Acute fulminating (malignant)
- IV. Exudative interstitial nephritis
 1. Acute nonsuppurative interstitial nephritis (p. 114)
 2. Pyelonephritis

The contrasting features of chronic nephrosis, glomerulonephritis, and arteriolar nephrosclerosis, the three more important clinical and anatomic types which terminate in renal insufficiency, are shown in Table 41, modified from a table of Van Slyke and his colleagues.

Acute Nephrosis

Acute nephrosis is a diffuse bilateral disease of the kidney, characterized by acute degenerative changes in the tubules, notably cloudy swelling, fatty metamorphosis, necrosis, and calcification.

Pathologic Anatomy. The kidneys are enlarged, and weigh from 175 to 250 gm. The capsule is tense and strips easily, leaving a smooth, pale gray, yellow, or pink surface. The shape is unaltered. The organ is flabby; the

* As quoted in Oertel, H.: *The Anatomic Histological Processes of Bright's Disease*. W. B. Saunders Company, Philadelphia, 1910.

parenchyma cuts with decreased resistance; and the substance bulges from the cut surface. The cortex is increased in thickness to 9 to 12 mm., and the pale cortex is sharply delineated from the darker medulla. The pars convoluta is prominent and grayish yellow. The glomeruli are inconspicuous. The pars radiata is narrow and light red. The medulla may contain yellow streaks. The pelvis and peripelvic fat are normal.

Microscopic examination reveals changes that are most conspicuous in the proximal convoluted tubules. The cells show many types of degenerative lesions: cloudy swelling, hydropic degeneration, hyaline droplets, fatty metamorphosis, necrosis, and calcification. The lumens are decreased in size and filled with an acidophilic debris free of cells. The glomeruli may show degenerative changes in the endothelium and epithelium, especially deposition of small droplets of fat, but there is no proliferation or infiltration of cells. The glomerular capsule frequently contains an acidophilic debris. The blood vessels are unaltered.

Causal Agents. The causes of acute nephrosis may be classified as exogenous and endogenous, or as chemical, infectious, and metabolic. Among the exogenous chemical agents are mercuric chloride, uranium nitrate, oxalates, tartrates, sulfonamides, and arsenic (see Chapter LXVII, p. 531). The infectious group includes the toxins of bacteria which are nephrotoxic. In most infectious disease there is some degree of nephrosis. The metabolic agents include the substances active in the toxemias of pregnancy and in obstructive jaundice (probably the bile salts).

Hypoxic Nephrosis

Under a wide variety of conditions a distinctive lesion of the kidney associated with renal insufficiency is observed and has usually been designated as lower nephron nephrosis. This term is not exact and the designation of hypoxic nephrosis is more revealing of cause and effect.

Pathologic Anatomy. The kidneys are enlarged, flabby, and generally pale in color. The cortex is increased in thickness, bulges from the cut section, and is moist. Although the microscopic changes vary slightly with the cause, the chronology of events given by Mal-

lory for examples following shock is typical. In eighteen to twenty-four hours there is lipid vacuolation of the epithelium of the ascending limb of Henle's loop. After twenty-four to thirty-six hours casts containing hemoglobin or myoglobin appear in the distal convoluted and collecting tubules. This is followed by slight dilatation of the tubules. Necrosis and early regeneration of the epithelium of the

rectly by spasm of the renal arterioles. For example, it is known that dissolved hemoglobin will produce such a spasm (Strauss).
In experimental animals a similar condition is produced by shunting of blood directly from the arcuate arteries into the medulla with consequent hypoxia of the cortex (Truetta, Barclay, Daniel, Franklin, and Prichard). It is possible that the long recognized anuria after

TABLE 41. ESSENTIAL FEATURES OF BRIGHT'S DISEASE

	Chronic Nephrosis	Glomerulonephritis	Arteriolar Nephrosclerosis
Nature of lesion.....	Degenerative	Inflammatory	Ischemic
Structure primarily affected..	Tubules, and in amyloid nephrosis glomeruli and arterioles	Glomeruli	Blood vessels
Anatomic changes.....	Degenerated tubular epithelium. Varying proportions of glomeruli may be destroyed; hyaline or amyloid. In amyloid type arteriolar walls are more or less infiltrated by amyloid material	Glomerular inflammation leading in terminal stage to nearly complete destruction. Also varying tubular degeneration and arterial changes	Arterioles are diseased, with contracted lumina, endarteritis, intimal hyperplasia, fatty degeneration, necrosis, in varying degree. Varying proportions of glomeruli destroyed
Clinical course.....	Insidious onset. Edema and proteinuria. No hypertension. May end in cure, death by intercurrent infection, or less frequently uremia	Acute onset. Either heals, improves to a latent condition, or progresses through an intermediate chronic state, usually edematous, with diminishing renal function, to terminate in uremia	Insidious onset. Marked hypertension. No edema unless cardiac. Death by cardiac failure, apoplexy, or uremia
Urinary sediment.....	Chiefly hyaline casts, few epithelial, fatty, granular, and waxy. No blood casts. Failure casts in cases with terminal uremia. Doubly refracting globules in lipoid nephrosis	Red cells in varying numbers. Blood, epithelial, and granular casts, in all stages except terminal. Hyaline casts in all stages. Broad "renal failure" casts in terminal	Chiefly hyaline casts

ascending limb and distal convoluted tubules are seen on the third to fifth day. After the fifth day there is rupture of tubules and formation of small granulomas, interstitial edema and infiltration of lymphocytes, and formation of thrombi in the small veins.
Causal Factors. The changes of lower nephron nephrosis are observed after hemolytic transfusion reactions, in blackwater fever, after transurethral prostatectomy, in shock, in heat stroke, in the crush syndrome, associated with diverse chemical poisonings, and in other conditions. It is difficult to define one common factor in all these conditions. Possibly it is hypoxia induced directly by shock, or indi-

operations on the urinary tract ascribed to a cysto-renal and reno-renal reflex is hypoxic nephrosis.
It is also probable that the rare massive infarction of the cortices known as symmetrical cortical necrosis (Duff and More) and seen in pregnancy and other conditions is an extreme degree of lower nephron nephrosis.
Clinicopathologic Correlation. Hypoxic nephrosis runs a course of two to twenty days with about half the deaths within six days (Lucké). The renal insufficiency is associated with azotemia, systemic edema, pulmonary edema, and, after the first few days, frequently hypertension. It is possible an associated car-

diac failure is related to a hyperpotassemia caused by renal failure. The direct cause of the renal insufficiency is not clear; it may be injury of epithelial cells, blockage of the tubules by casts, or some other factor.

Lipid Nephrosis

Lipid nephrosis is a rare chronic disease of children and young adults, usually insidious in onset, characterized by anasarca, albuminuria, waxy pallor, decreased protein and increased

form of the characteristic maltese cross. Similar globules of the doubly refractile fat are found in the lumen, embedded in an acidophilic debris. The desquamation of cells thus leads to the appearance of fat in the urinary sediment—an important diagnostic feature of the disease. In the glomeruli there is slight thickening of the basement membrane, and in some instances slight proliferation of endothelial cells (Bell). The interstitial tissue and the blood vessels show no significant pathologic change.

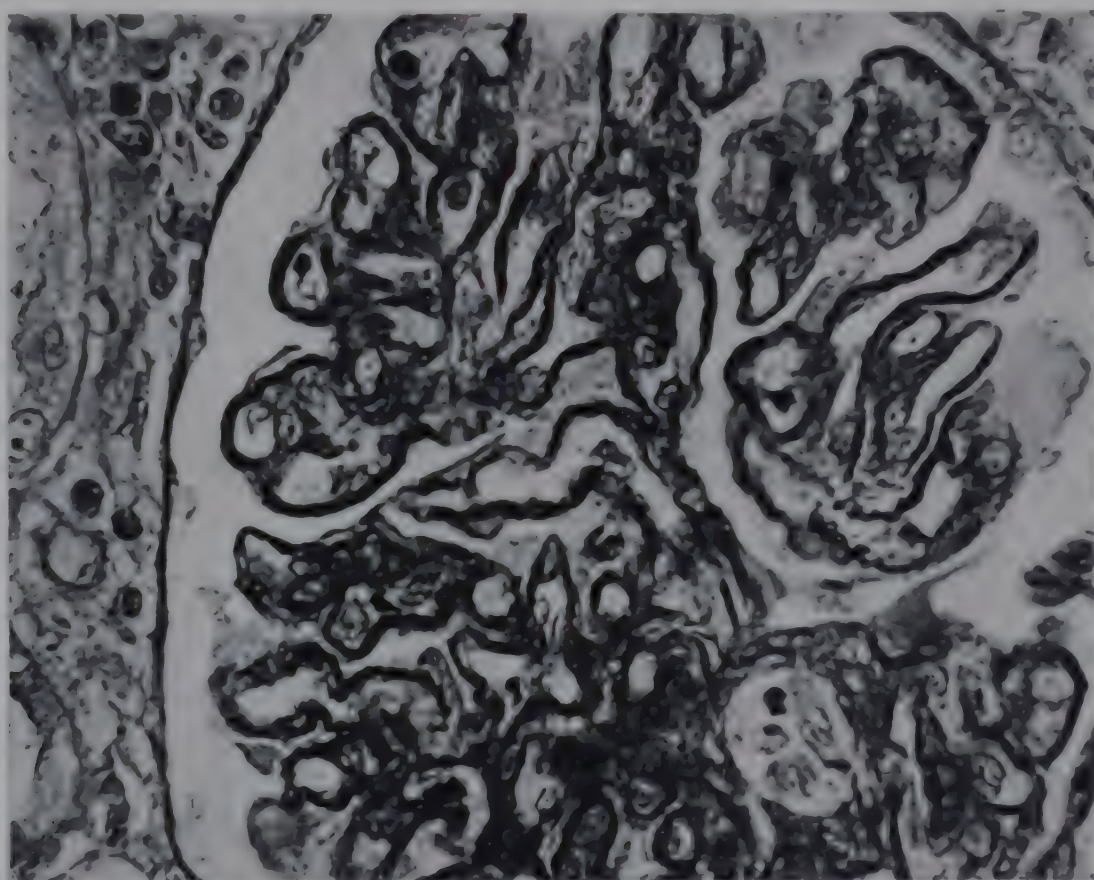


Fig. 357. Thickening of glomerular basement membrane in lipid nephrosis.

lipid content of the plasma, decreased metabolic rate, and good renal function (Leiter).

Pathologic Anatomy. The kidneys are slightly to moderately enlarged, and slightly softer than normal. The color is mottled yellow-red. The capsule strips with ease, leaving a smooth surface. The cortex is slightly increased in thickness and streaked with yellow. The architecture is distinct, and there are no essential changes in the medulla, pelvis, or peripelvic fat.

The tubules are slightly dilated. The epithelial cells, especially of the proximal convoluted tubules, show various degenerative changes such as cloudy swelling and hydropic degeneration. In the cells of the proximal convoluted tubules there are numerous vacuoles filled with both isotropic and anisotropic fat. The latter appears with polarized light in the

Changes in the other viscera are inconstant and related only to the immediate cause of death. Few patients die of renal insufficiency. The commonest terminal complication is an acute purulent peritonitis caused by the pneumococcus and not related to any respiratory infection. Less common causes of death are pneumonia and empyema.

Incidence. Lipid nephrosis is a disease of children and young adults, with only a rare patient over forty. There is no sex or racial predisposition.

Biochemical Lesions. Chemical studies of the blood reveal an increase of lipids, especially cholesterol and cholesterol esters; a decrease of proteins, especially albumin, with a reversal of the albumin-globulin ratio; and a decrease of calcium. There is no constant deviation from normal of the cellular elements,

electrolyte balance, or total blood volume. Just before and during a crisis there is a low value for plasma amino acid (Fahr). The transudates have a low specific gravity—less than 1.010—and a protein content of less than 0.1 per cent. The lipid in the kidney is largely cholesterol esters. Renal function remains essentially normal.

Physiologic and Chemical Relations. *Urinary loss of protein* varies from a few to over 20 gm. a day, and from 85 to 95 per cent is albumin. This constant loss is the principal factor in the *decrease of plasma protein*, and the hypoproteinemia is in turn the chief factor in precipitating the *edema*. The osmotic pressure of the plasma proteins is normally 31 to 37 cm. of water. Each gram of albumin exerts an osmotic pressure of about 7.50 cm., and each gram of globulin 1.95 cm. At values between 24 and 27 cm., edema may be present. In lipid nephrosis, the total protein of 4 gm. per 100 cc., with 1 gm. of albumin, may have an osmotic pressure of only 13 cm. of water. By and large, the appearance and disappearance of edema is directly correlated with the relative and absolute levels of the plasma proteins. The reason for the *elevation of plasma cholesterol* is not known with certainty. So far as can be determined, it does not represent any basic disturbance in lipid metabolism. It is possible that cholesterol lightly bound to protein is not excreted and hence accumulates. An explanation of the *low basal metabolism*, —10 to —20, has not been established, but there does not appear to be hypothyroidism. The increased tolerance for thyroxin is seen in many types of edema.

Pathogenesis. The absence of significant constant changes in other organs indicates that lipid nephrosis is a primary renal disease and not a general disturbance in the metabolism of either proteins or lipids. Experimental attempts to reproduce the disease have used hypoproteinemia (induced by low protein diet or plasmapheresis), hypercholesterolemia (by feeding), and the nephrotoxic properties of extracts of the pneumococcus (Blackman). None of these procedures has quite duplicated the anatomic changes of lipid nephrosis.

Some pathologists are impressed with the minimal glomerular change, and regard lipid nephrosis as one type of glomerulonephritis (Bell). This view receives some support from the frequent association of the clinical and an-

atomic changes of lipid nephrosis with subacute and chronic glomerulonephritis.

Clinicopathologic Correlation. The course in lipid nephrosis is irregular. There are relapses from time to time, and frequently these are fulminating and end in pneumococcal peritonitis. The first sign of a crisis is a precipitous fall in the amino acids of the blood, and the administration of these substances has some beneficial effect. About 50 per cent of patients die of some complication of lipid nephrosis, or go on to develop glomerulonephritis, and die of uremia. Another 25 per cent apparently recover from the disease, and during young adulthood show no evidence of renal disease. The final 25 per cent continue with the signs and symptoms of lipid nephrosis (Schwarz, Kohn, and Weiner).

Glomerulonephritis

Pathologic Anatomy. It should be remembered that the division of glomerulonephritis into acute, subacute, and chronic is entirely artificial, and that all transition stages between the three are seen.

Acute Glomerulonephritis. The kidneys are greatly enlarged, and frequently weigh over 300 gm. In fact, the larger the kidneys the more likely the diagnosis of acute glomerulonephritis. The capsule is under great tension and strips with ease, leaving a smooth red surface. Throughout the red background there are numerous petechiae, corresponding in number to the glomeruli. The renal parenchyma is soft and flabby and cuts with decreased resistance. From the cut surface a quantity of red fluid exudes. The cortex is increased in thickness, and throughout the pars convoluta most of the glomeruli are visible as slightly elevated red dots. The blood vessels in all parts of the kidney are dilated. The pelvis and peripelvic fat are unaltered.

The pathologic changes involve all structures of the kidney. The glomeruli show a variety of changes, classified as exudative or proliferative, and intercapillary or capsular. The endothelial cells of the glomerular capillaries are increased in number and swollen so that the lumens are effectively blocked. Mononuclear cells and polymorphonuclear leukocytes also contribute to the blocking of the capillaries. There is a less conspicuous proliferation of the epithelial cells of the glomerular

TABLE 42. DIFFERENTIAL DIAGNOSIS OF ANATOMIC FORMS OF BRIGHT'S DISEASE

Lesion	Weight of Kidney in Gm.	Adherence of Capsule	Surface	Color	Consistency	Thickness of Cortex in Mm.	Glomeruli on Cut Surface	Architectural Pattern of Cut Surface	Ratio of Pars Convoluta to Radiata	Pelvis and Peripelvic Fat
Acute nephrosis.....	175-250	—	Smooth	Pale	Soft, flabby	9-12	Inconspicuous	Prominent	3 or 4 : 1	Normal
Hypoxic nephrosis.....	175-250	—	Smooth	Pale	Flabby	9-11	Inconspicuous	Prominent	3 : 1	Normal
Amyloid nephrosis.....	175-225	—	Smooth	Pale glossy	Firm	8-10	Gray, translucent dots	Obscured	2 : 1	Normal
Lipid nephrosis.....	175-250	—	Smooth	Yellow-gray	Soft	8-10	Inconspicuous	Normal	3 : 1	Normal
Acute glomerulonephritis.....	200-350	—	Smooth	Red	Flabby	10-14	Red, elevated, prominent	Prominent	3 or 4 : 1	Normal
Subacute glomerulonephritis.....	175-275	±	Smooth	Pale mottled	Firm	8-10	Gray, elevated	Inconstant	2 or 3 : 1	Normal
Chronic glomerulonephritis.....	as low as 25	+++	Irregularly nodular	Pale	Very firm	2-5	Inconspicuous	Obscured	1 or 2 : 1	Slightly dilated, fat increased
Arterial nephrosclerosis.....	125-175	Focally	Focal V-shaped scars	Inconstant	Firm in scars	Normal except in scars	Normal except in scars	Obscured in scars only	2 : 1	Normal
Arteriolar nephrosclerosis.....	40-150	Variable	Uniformly nodular, rarely smooth	Normal or pale	Firm	4-7	Inconspicuous	Slightly obscured	Normal except in scars	Slightly dilated, fat increased
Malignant nephrosclerosis.....	100-200	±	Finely nodular petechiae	Mottled yellow-red	Firm	7-10	Some red elevated	Slightly obscured	3 : 1	Normal size, petechiae
Chronic pyelonephritis.....	25-125	Focally	Focal U-shaped scars	Inconstant	Firm in scars	Normal except in scars	Normal except in scars	Obscured in scars only	Normal except in scars	Dilated, thickened

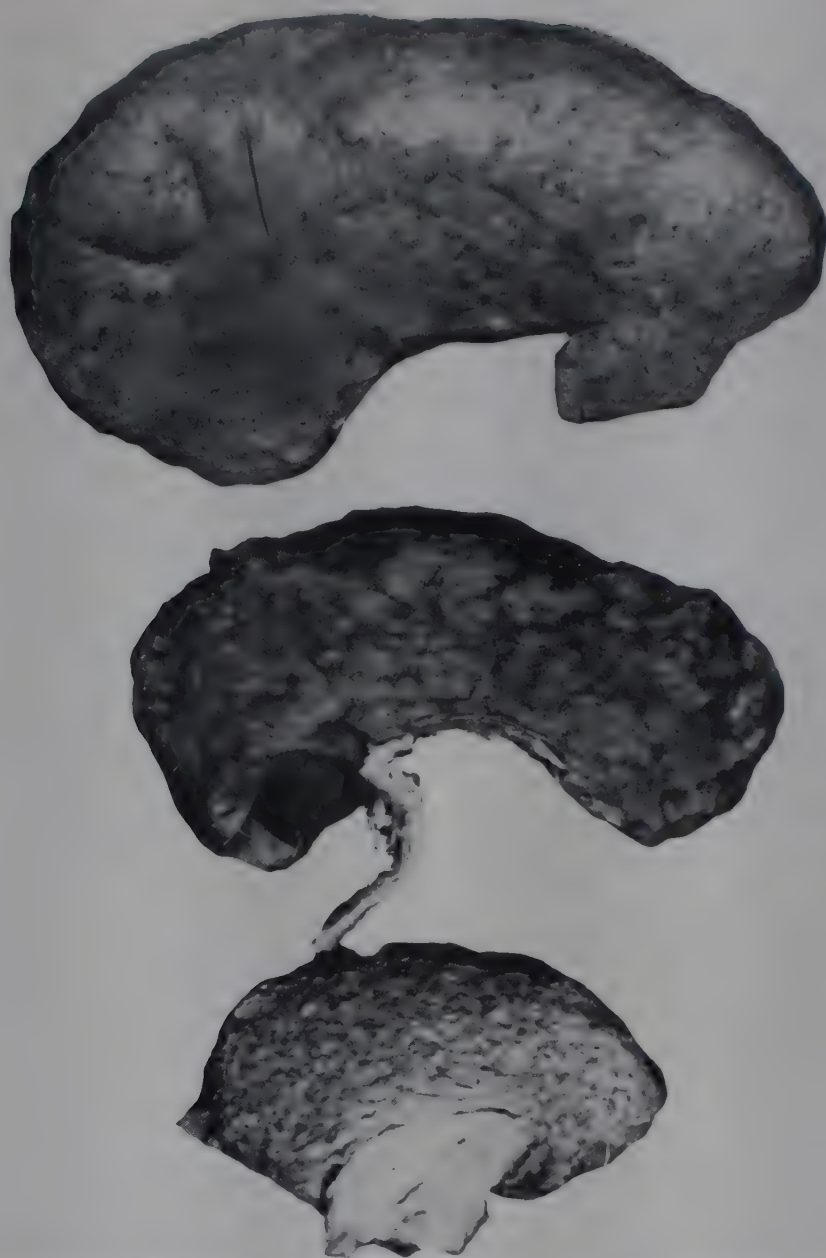


Fig. 358. Surface of kidney showing comparative size and nature of surface in (from above downward) acute glomerulonephritis, chronic pyelonephritis, and chronic glomerulonephritis.

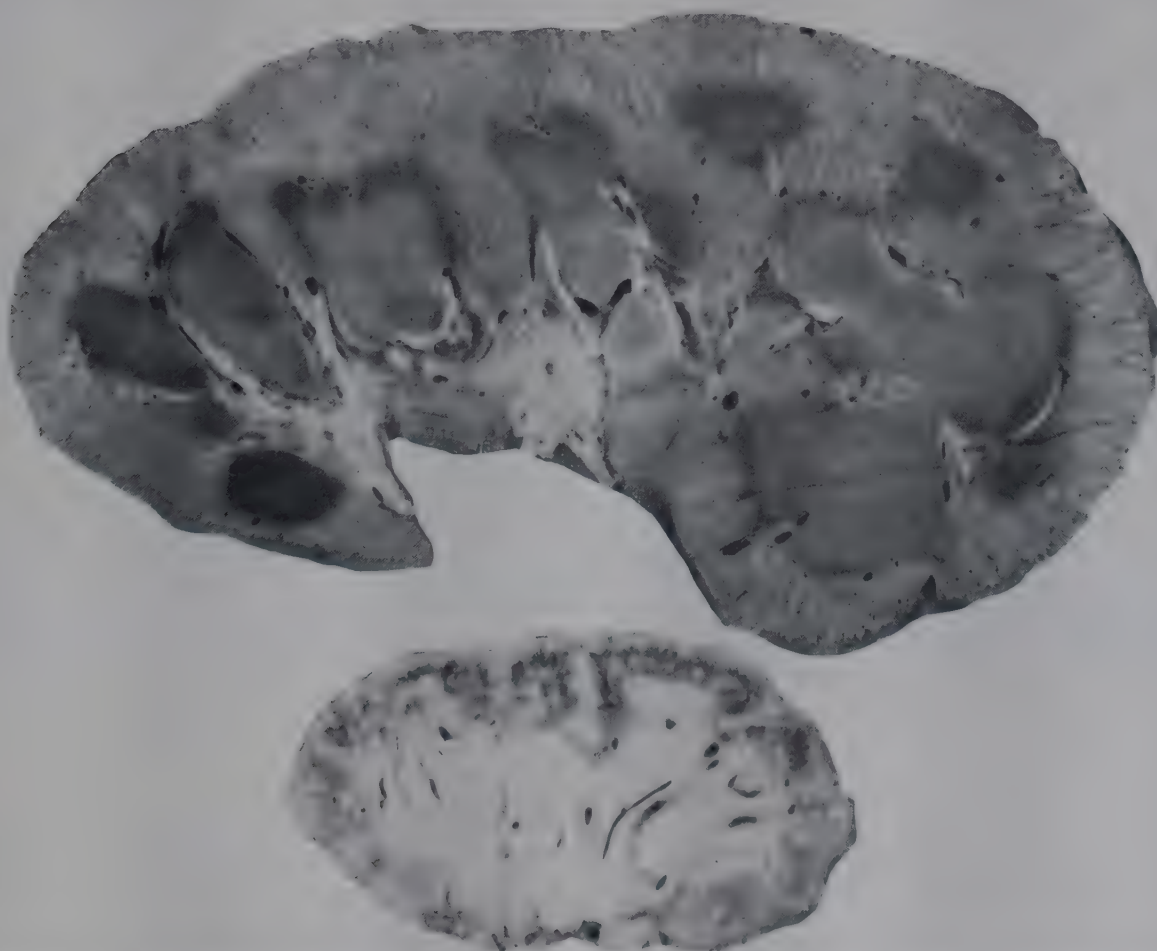


Fig. 359. Cut surface of the kidney in acute glomerulonephritis (above) and chronic glomerulonephritis.

tuft. In the capsular type of change the lesion is essentially proliferative. The epithelial cells of the parietal layer of Bowman's capsule increase in number and form a crescent-shaped

Bowman's space. Less frequently there are mononuclear cells and leukocytes in the capsular space and in the lumen of the proximal convoluted tubules. The tubular epithelium

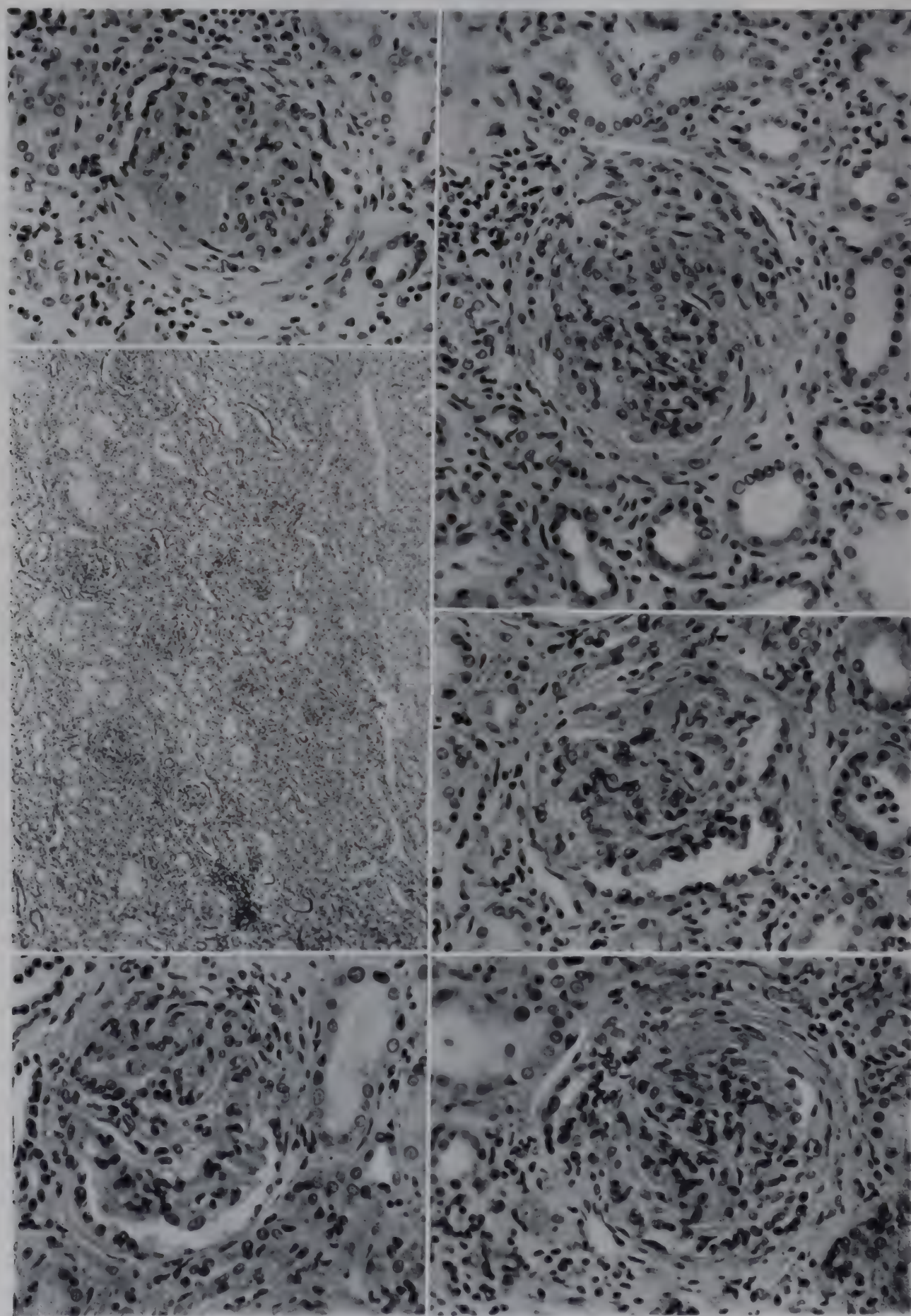


Fig. 360. Chronic glomerulonephritis. Five glomeruli in the low-power field at the left.

mass with the convexity of the crescent directed toward the vascular pole. The proliferating cells come in contact with similar cells of the glomerulus, and there is a union between the two, thus, obliterating a part or all of

shows slight to moderate degenerative change. The interstitial tissue is edematous and infiltrated with mononuclear cells and a few leukocytes. The blood vessels are dilated, but not otherwise abnormal.

Subacute Glomerulonephritis. This represents either the beginning of healing in acute glomerulonephritis or a primary, less severe type of inflammation. The kidneys are increased in size, but not so much as in acute glomerulonephritis. The capsule usually strips with ease, but there may be isolated adhesions. The surface is smooth, but the kidney substance is increased in consistency and pale. On the cut surface the glomeruli project as small, gray, translucent dots. The architectural pattern is normal or slightly obscured. The pars convoluta is prominent and the pars radiata inconspicuous and red. The pelvis and peripelvic fat show no change.

The glomeruli show evidence of a less severe inflammation of longer duration. The exudation of cells is less conspicuous and proliferation is the predominant change. Between the proliferating epithelial cells there is a deposition of collagen, and there are numerous adhesions between the glomerular tuft and the parietal layer of Bowman's space. The connective tissue beneath the epithelium about each glomerulus is increased in amount. Within the glomerulus many capillaries are completely occluded by a deposition of fibrin or of collagen. The interstitial tissue shows slight edema, but no significant cellular infiltration. The tubules may show slight degenerative change, or may contain numerous droplets of fat, some of which are anisotropic.

Chronic Glomerulonephritis. The kidneys are characteristically reduced in size, and the smaller the kidney the more likely the diagnosis of chronic glomerulonephritis. The capsule strips with difficulty, and the surface is coarsely and irregularly granular. The granules vary in size from one to several millimeters, and are yellow. The intervening tissue is pink or gray and firm. The substance cuts with increased resistance. The cortex is reduced in thickness, and the architectural pattern of both the cortex and medulla is in large part obliterated. The glomeruli are not visible. The pelvis is slightly dilated, and there is an increase of the peripelvic fat.

Many of the glomeruli have been completely replaced by collagenous connective tissue, and are seen in sections as round, fibrous structures. Other glomeruli show increased lobulation, fibrous adhesions between the glomerulus and the capsule, and loss of capillaries. In the regions of scarring, many of the tubules have

been destroyed, and there is infiltration of mononuclear cells, plasma cells, and lymphocytes. In the projecting nodules the tubules are dilated and lined with cuboidal or columnar acidophilic or basophilic cells, showing some type of degenerative change. The blood vessels are thickened, especially arterioles. In the medulla there is an increase of connective tissue. The pelvis shows no deviation from normal.

By microdissection of a partially macerated kidney the individual nephrons may be isolated and studied. Although the parenchymal distortion may proceed in many ways, the end results of all are remarkably similar (Oliver).

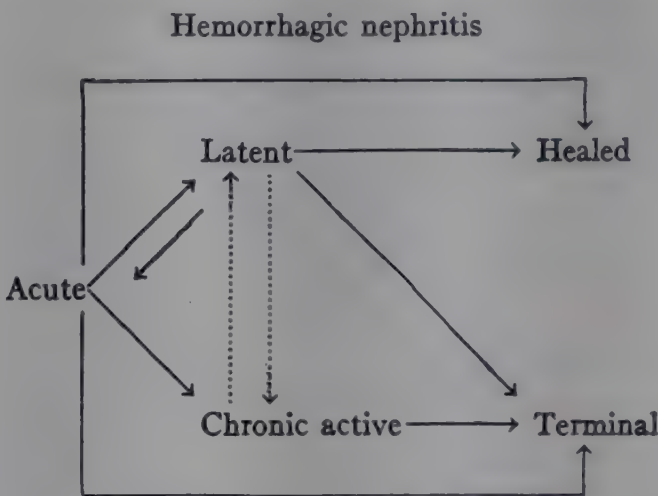


Fig. 361. Relation of types of glomerulonephritis. (Van Slyke: Medicine, Vol. 9.)

Relation of Types of Glomerulonephritis. In the progress of glomerulonephritis in any given patient the stages of acute, subacute, and chronic are not sharply separated. The relation between the anatomic types and the clinical stages of latent, active, and terminal is shown in Fig. 361, taken from the paper by Van Slyke and his colleagues. The concepts illustrated are basic to any understanding of the events as they unfold during the course of the disease.

The fate of a person who develops acute glomerulonephritis cannot be predicted with certainty. From 5 to 10 per cent die in the acute stage, 10 to 20 per cent develop chronic glomerulonephritis, 20 to 30 per cent have latent glomerulonephritis, and 45 to 65 per cent are apparently cured (Hayman and Martin). About a fourth of those with chronic glomerulonephritis have acute exacerbations, frequently following some streptococcal infection (Seegal, Lyttle, Loeb, Jost, and Davis).

Glomerulitis. In about half of the patients who have died of an acute or chronic infectious disease there are proliferation of the

glomerular endothelium and lodgment of mononuclear cells in the capillaries (Bell). The lesions are most prominent in subacute bacterial endocarditis and puerperal sepsis. In advanced stages they are indistinguishable from those of acute diffuse glomerulonephritis.

Nephrotic Syndrome in Glomerulonephritis. Some patients with the clinical picture of glomerulonephritis, especially in the subacute stage, show massive edema and all of the other clinical manifestations of lipid nephrosis. The kidneys are enlarged and mottled yellow-red. The tubules show degenerative changes, and the cells contain excessive amounts of lipid, some of which is anisotropic.

Some regard this condition as a combination of two distinctive diseases, while others

focused on the cause of acute glomerulonephritis.

Viewed on a chronologic basis, 90 per cent of all patients give a history of some infection in the immediate past. About 70 per cent of these infections are of the upper respiratory tract: sore throat, tonsillitis, otitis media, sinusitis, and scarlet fever (Hayman and Martin). The number of persons with these diseases who develop acute glomerulonephritis is, however, extremely small: 0.2 per cent in upper respiratory infection (Kayser-Petersen and Schwab); 0.7 per cent in pneumonia (Segal); and 1 per cent in rheumatic fever (Baehr and Schifrin).

The most common offending bacterium in all of these infections is the hemolytic streptococcus. The mechanism by which a strepto-

TABLE 43. AGE DISTRIBUTION IN GLOMERULONEPHRITIS

Age (Years)	Acute Cases	Subacute Cases	Chronic Cases	
			With Azotemia	With Edema
0-10.....	12	1	1	9
10-20.....	13	3	10	3
20-30.....	7	3	30	6
30-40.....	14	2	33	10
40-50.....	7	2	23	6
50-60.....	14	3	10	3
60-70.....	11	1	8	2
Over 70.....	3	1	2	1
Total Cases.....	81	16	117	40

look upon lipid nephrosis as a form of glomerulonephritis (Bell).

Incidence. Glomerulonephritis constitutes less than 1 per cent of the causes of death in the United States. Higher figures in vital statistics are based on the clinical confusion between nephritis and nephrosclerosis. There is no predilection for either sex, and persons of all ages are affected. The age at the time of death in the various types is illustrated in statistics compiled from the various papers of Bell (Table 43). By comparison with arteriolar nephrosclerosis, in which 90 per cent or more of the patients are over forty years of age, 60 per cent of patients with glomerulonephritis are under forty.

Causal Factors. It is evident from the facts given in the preceding paragraph that a search for the cause of glomerulonephritis must be

coccal infection produces nephritis, and the reason for the variation in the course of the disease in different people, are matters of theory. According to our present knowledge there are three possibilities: (1) the bacteria are carried to the kidney by the blood and excite the inflammation; (2) toxins of the bacteria act on the glomerular tissue; and (3) some distinctive type of antigen-antibody response is elicited.

The objection to the first is that bacteria can rarely be demonstrated in the inflamed tissue. An objection to both the first and second is that a similar lesion cannot be produced in animals with any constancy by the postulated mechanism. Experimental studies on autosensitization to a mixture of kidney and streptococcal toxin have given promising results. A mechanism of this type would explain

many known facts about glomerulonephritis, especially an indirect relation to streptococci (Schwentker and Comploier).

Nephritis in Animals. Most laboratory animals, especially older ones, have a type of interstitial nephritis. In dogs and rabbits, minimal lesions may be observed in over 50 per cent of all animals. There are lymphocytic infiltration, focal fibrosis, and tubular dilatation.

Nephrosclerosis

Nephrosclerosis is the change in the kidneys produced by decrease in blood supply

considerable percentage of cases there is a plaque in the wall of the aorta at the orifice of the renal artery, with consequent reduction in the size of the orifice.

The most conspicuous change seen microscopically is a thickening of the smaller arteries up to and including the afferent glomerular arterioles. This thickening may take the form of intimal hyperplasia, of medial hyperplasia, or of medial and intimal hyalination. The lumens are decreased in size. The glomeruli are relatively acellular, and there is increased lobulation. The glomerular basement membrane is greatly thickened (McGregor).

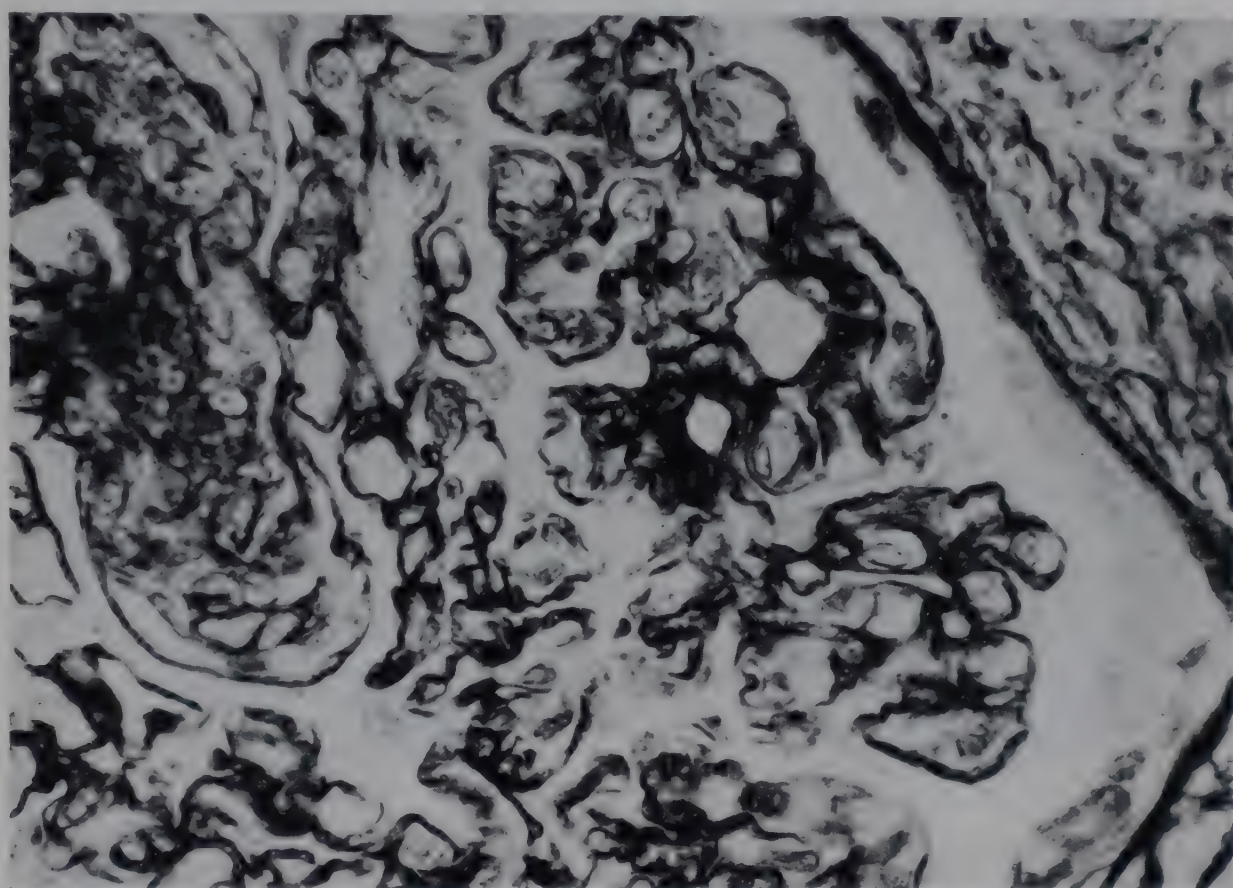


Fig. 362. Thickening of basement membrane of glomerular capillaries in arteriolar nephrosclerosis.

induced by disease of the blood vessels. It is convenient to divide nephrosclerosis into two types: arterial and arteriolar, in which the arteries and arterioles respectively are involved.

Arteriolar Nephrosclerosis. In the usual case of arteriolar nephrosclerosis the kidneys are moderately reduced in size. The capsule strips with slight difficulty, and tears the underlying renal substance. The surface of the kidney is granular, the granules averaging 2 to 3 mm. in diameter and projecting above the depressed areas not over 1 mm. The parenchyma is reduced in thickness, and this reduction is largely at the expense of the cortex. The blood vessels on the cut section stand out prominently. The pelvis is slightly dilated, but there is no thickening of the mucosa. In a

The fibrous tissue about Bowman's capsule is prominent. The interstitial tissue throughout is increased, and there is slight lymphocytic infiltration. The tubules show no constant alteration. The apparatus of Goormaghtigh about the vascular pole of the glomeruli shows no constant deviation from normal (Kaufmann).

Arterial Nephrosclerosis. The kidneys are of the usual size or slightly decreased. Over the surface are deep V-shaped scars extending to the corticomedullary junction. About and in each scar there are fibrosis, loss of tubules, and hyalination of the glomeruli. The renal substance between the scars shows no significant change. So far as can be determined the presence of a few arterial scars in a kid-

ney is of no clinical significance, and there is no demonstrable relation to hypertension.

Clinicopathologic Correlation. Arterial nephrosclerosis apparently is of little or no significance; at least it is only rarely associated with hypertension. In most instances arteriolar nephrosclerosis is a part of a generalized disease of small vessels and is associated with hypertension (p. 753). In some patients with nephrosclerosis the clinical

surface is finely granular, and the capsule strips with only slight difficulty. The kidney substance is firm and red. The cortex is slightly reduced in thickness, and the renal arteries on the cut section appear prominent and stiff. Distributed over the surface of the kidney and on the cut section there are numerous small punctate hemorrhages, 1 mm. in diameter. These petechiae are larger and more prominent than those in acute glomerulonephritis.

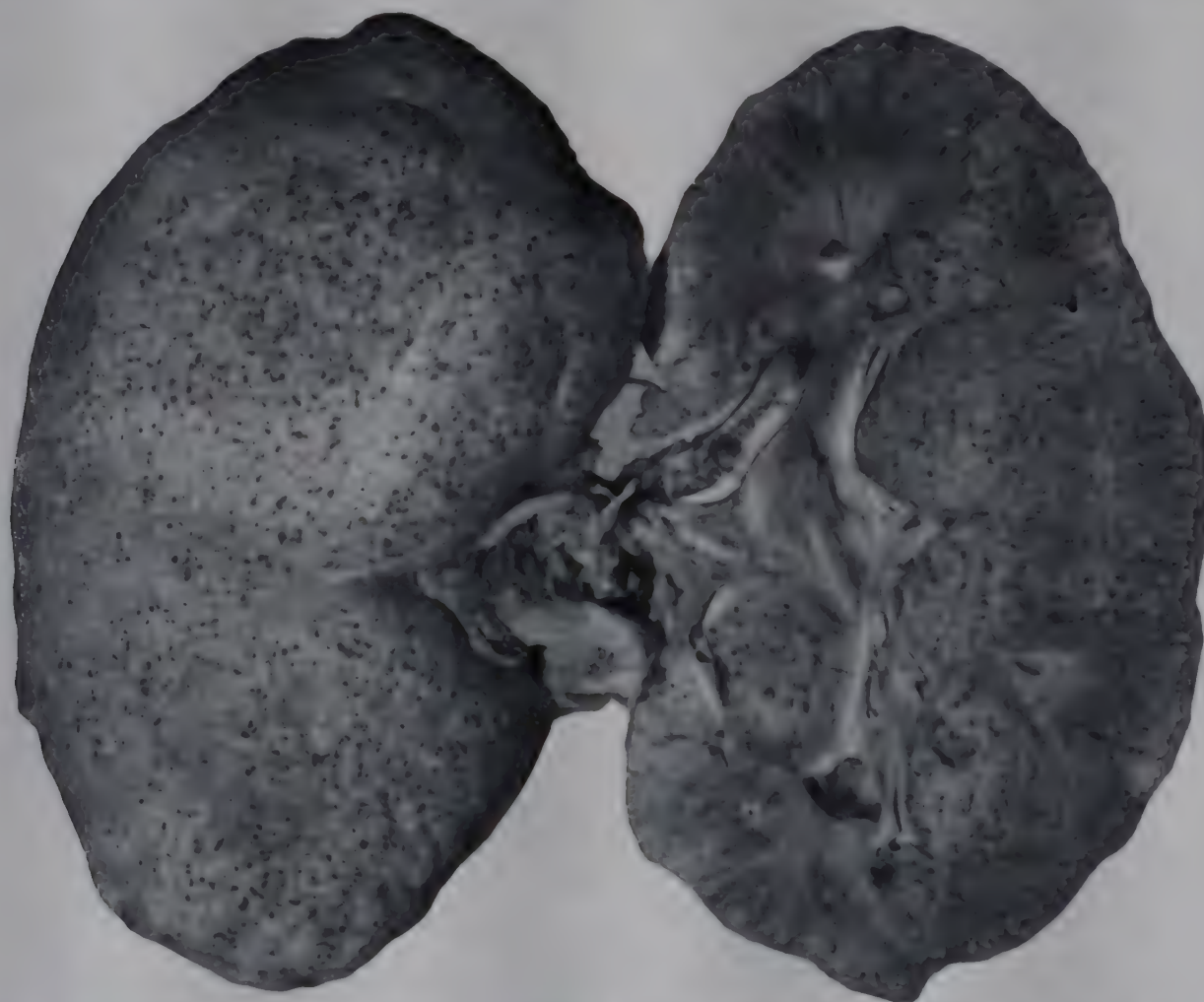


Fig. 363. Malignant nephrosclerosis. (Armed Forces Institute of Pathology, Neg. No. 63551.)

course is suddenly accelerated and there is necrosis of the arterioles which is discussed in the next section.

Malignant Nephrosclerosis

In some persons who have had hypertension for a period of years without serious signs or symptoms, a sudden acceleration of the process appears and death occurs within a few weeks or months. The onset of this phase of the disease, known as "malignant nephrosclerosis" or "malignant hypertension," frequently follows some acute infectious disease, exposure to adverse environmental conditions, or pregnancy.

Pathologic Anatomy. At autopsy the kidneys present a characteristic picture. They are normal in size, or somewhat smaller. The

Other points of distinction are the size and the consistency of the kidney.

The arterioles throughout all parts of the kidney are thickened, and the lumens are decreased in diameter. In the walls of many arterioles there are foci of necrosis and hemorrhage. In an occasional case the necrosis of the walls of the arterioles is extensive and associated with an acute inflammation involving all of the coats of the arteriolar wall. Within the lumen are hyaline thrombi, particularly in the afferent arterioles of the glomeruli. Parts of glomeruli or entire glomeruli show the pathologic changes of infarction. Within the proximal convoluted tubules and in Bowman's space there is hemorrhage. The tubular epithelium shows a variable degree of cloudy swelling and fatty degeneration. There is a slight increase of interstitial connective

tissue with lymphocytic infiltration (Klemperer and Otani).

There are similar but less conspicuous changes in the other arterioles of the body, particularly in the pancreas and the spleen. In the spleen the centers of the follicles undergo necrosis and are often grossly visible as pale-gray, translucent areas. Recent or old hemorrhages into the retina are common.

Pathogenesis and Experimental Observations. The exact pathogenesis of malignant hypertension in man is not clear, but the ob-

ritis most carefully recognize four types: acute, chronic, healed, and healed and recurrent (Weiss and Parker).

Acute Pyelonephritis. The kidneys are usually enlarged, and throughout the cortical substance there are numerous small abscesses, 1 to 2 mm. in diameter. In the medulla, there are narrow yellow streaks, representing supuration in this structure. The pelves are reddened and slightly dilated, and the mucosa is covered by an exudate. In the early stages, the infiltration with polymorphonuclear leuko-

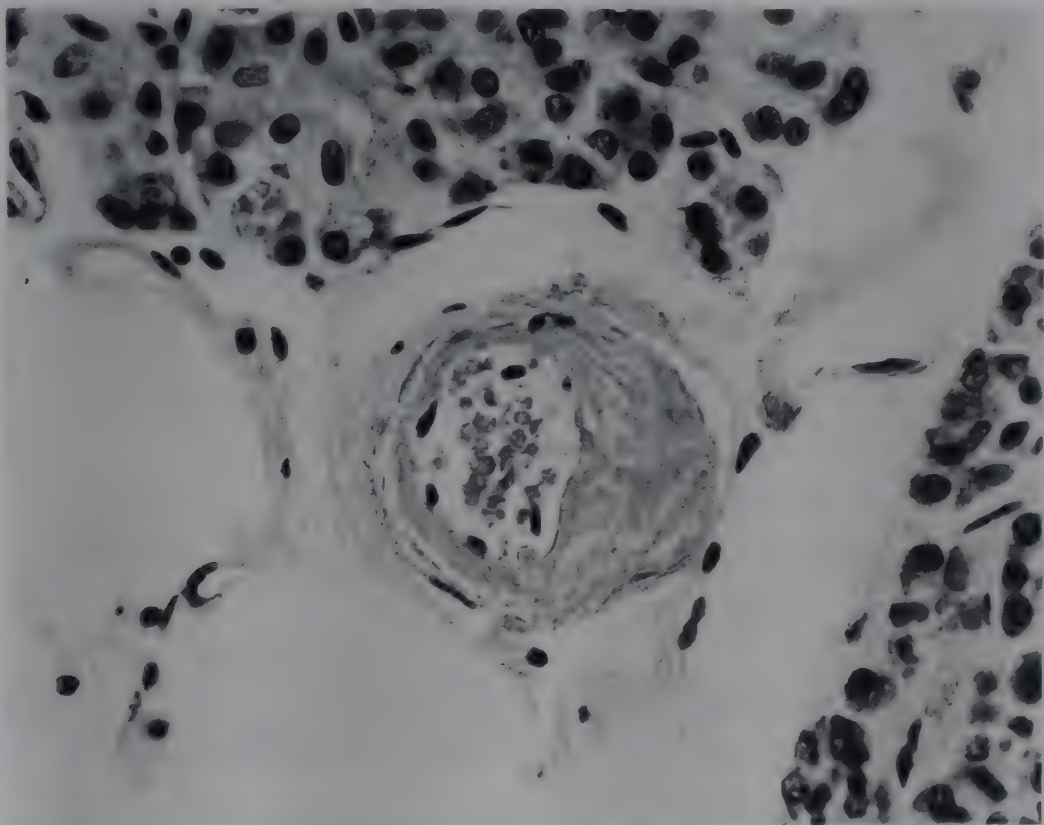


Fig. 364. Necrosis of wall of arteriole in pancreas.

servations of Goldblatt in experimental animals throw considerable light upon the problem. In dogs with partial constriction of the renal arteries and consequent hypertension, the pathologic picture of necrosis of arteries does not develop unless the animal is suffering from both hypertension and renal insufficiency. In the experimental animal there is no hypertension within the kidneys beyond the clamp on the renal arteries, and consequently the necrotizing lesions in the arterioles do not develop within the kidney of the dog. Comparison of these observations with the course and nature of the disease in man would indicate a similar pathogenesis—the combination of hypertension and uremia.

Pyelonephritis

Pathologic Anatomy. Those who have studied the pathologic anatomy of pyeloneph-

cytes is most prominent in the glomeruli, and in the periglomerular lymphatics. With further progress of the disease, many tubules become filled with leukocytes and there are degenerative changes in the tubular epithelium. The pelvic epithelium is in part necrotic.

Chronic Pyelonephritis. The kidneys may be enlarged, normal, or reduced in size. Over the surface, there are one or more discrete, depressed regions with sloping sides and a flat base. The capsule over these is adherent. The intervening surface is smooth or slightly nodular. The depressed scars involve the cortex and characteristically extend to the corticomedullary junction. There may be small abscesses throughout any part of the kidney. The wall of the pelvis is thickened and congested, and the cavity is partially or completely filled with an inflammatory exudate. In the scarred regions, there is an increase of interstitial

connective tissue and a loss of parenchymal elements, both tubules and glomeruli. The fibrous tissue is infiltrated with lymphocytes and a few leukocytes. The remaining tubules

increase of fibrous tissue, infiltrated with lymphocytes and plasma cells. There is no evidence of activity as seen by the presence of leukocytes.

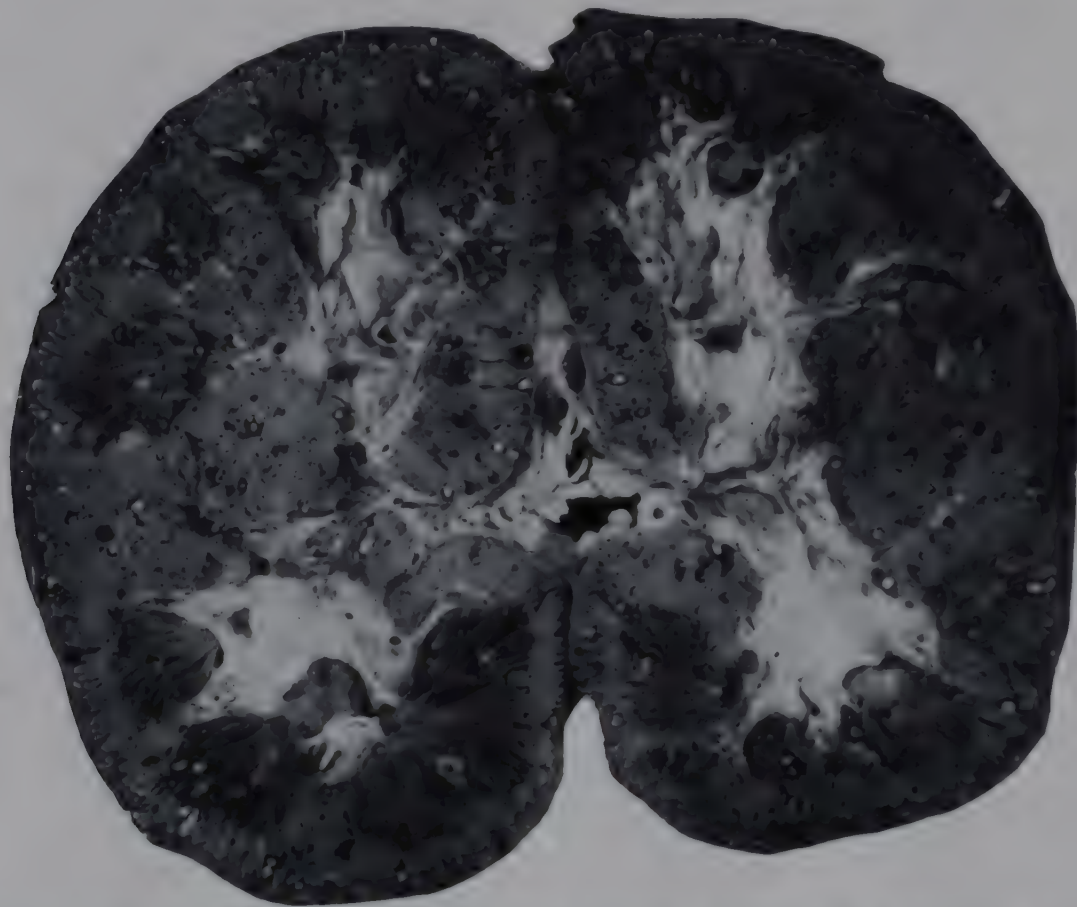


Fig. 365. Multiple abscesses of the kidney. (Armed Forces Institute of Pathology, Neg. No. 64688.)

are filled with hyaline casts. The blood vessels are thickened. In the uninvolved regions, the structure is essentially normal. In the peripelvic tissue, there is an increase of connective tissue and an infiltration with lymphocytes and plasma cells.

In many persons, increasing with age, there are small scars on the surface of the kidney from 1 to 3 mm. in diameter, which microscopically show all the characteristics of healed pyelonephritis.

Healed and Recurrent Pyelonephritis. The pathologic picture in this type is combination of healed pyelonephritis and acute pyelonephritis (Weiss and Parker).

Lesions of the Ureter and Bladder. In most cases of acute and chronic pyelonephritis, there is an associated ureteritis and cystitis. The mucous membrane is swollen and red, and the fluid within the lumen is cloudy. In chronic arteritis, the ureteral wall is thickened, the lumen is dilated, and the ureter increased in length, so that it is kinked.

Pathogenesis. Three theories have been proposed to explain the mode of entrance of bacteria into the kidney in pyelonephritis: (1) That bacteria ascend through the lumen of the ureter from the bladder; (2) that the ascent of the bacteria is through the peri-ureteral lymphatics; (3) that the bacteria are brought to the kidney by the blood. The bulk of present-day evidence supports the last.

Role of Obstruction. In man, pyeloneph-

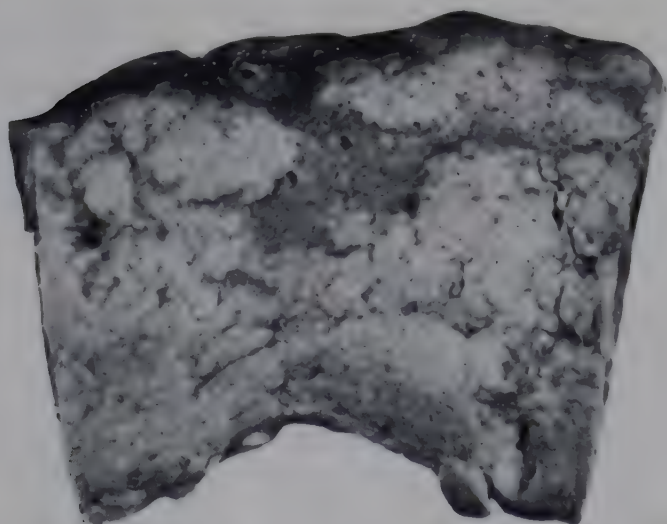


Fig. 366. Broad flat-based scars of kidney in chronic pyelonephritis.

Healed Pyelonephritis. The kidneys are reduced in size, and over the surface are numerous flat-based scars. The pelves are dilated. The remaining tubules in the involved region are filled with hyaline casts and there is an

ritis is usually associated with some type of obstruction: a deep caudal calyx, an accessory renal artery compressing the ureter, renal lithiasis, or some congenital anomaly of the urinary tract. In rabbits, chronic pyelonephritis can only be produced by a combination of temporary ureteral obstruction and intravenous injection of colon bacilli or other bacteria (Mallory, Crane, and Edwards).

tous cellulitis of the soft tissues about the bladder (Gillies), represent a similar phenomenon.

Perinephric Abscess. Acute pyelonephritis may spread to the perinephric tissues, or an abscess may rupture through the capsule. Pus accumulates in cavities and there is a cellulitis of the adjacent tissue. *Escherichia coli* can be cultured from most cases. A similar condition in association with bacteremia or pyemia is

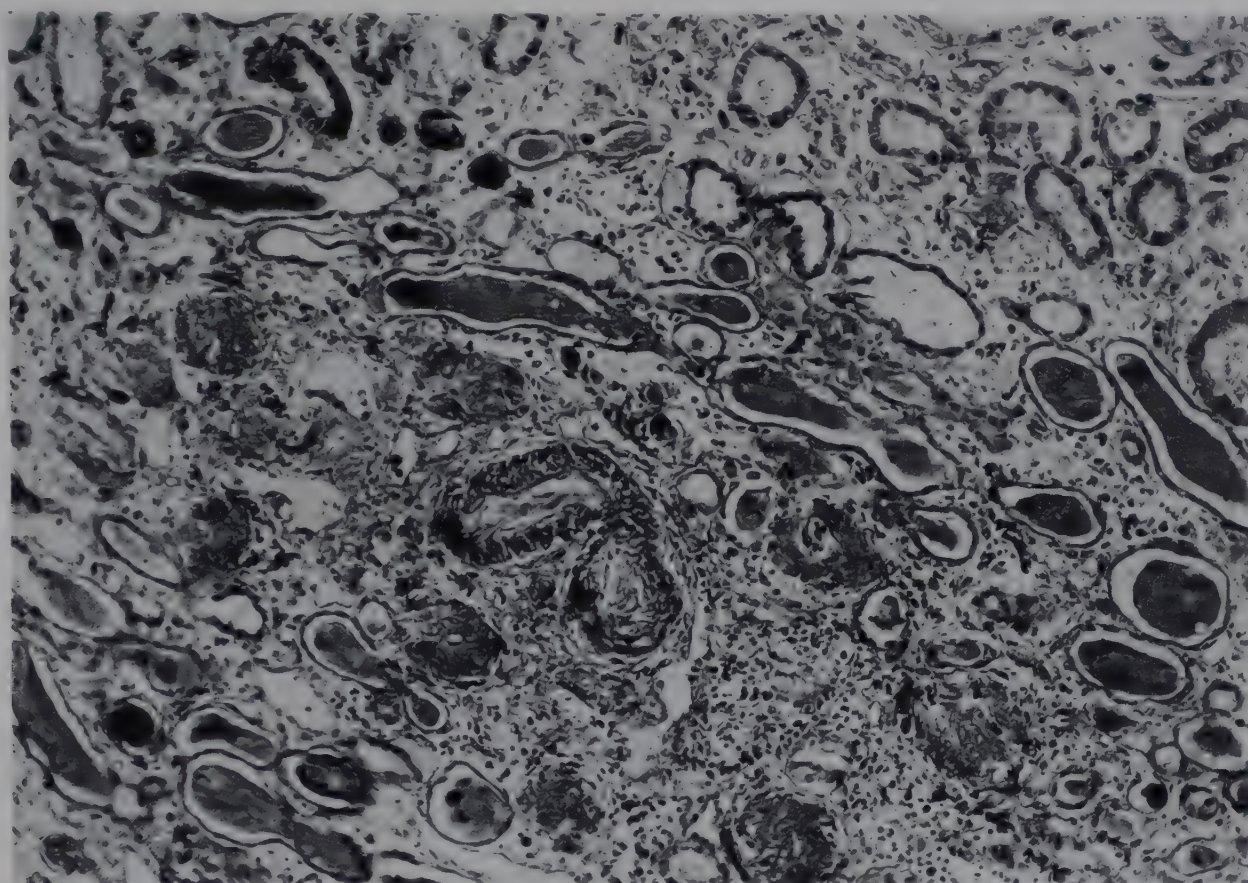


Fig. 367. Chronic pyelonephritis. Note interstitial fibrosis, cellular infiltration, hyaline casts, and thickened blood vessels.

Pyuria in Children. The most common cause of pyuria in children is a pyelonephritis. In the chronic types, there are the characteristic lesions in the kidney, and usually some form of ureteral obstruction. In acute types, there are numerous small foci of cellular infiltration in the cortex, with or without abscess formation. Pyelitis—an inflammation of the renal pelvis—probably does not exist as a separate entity (Wilson and Schloss).

Urinary Infection in Patients with Diabetes. About 20 per cent of patients with diabetes have an anatomically demonstrable infection of the urinary tract caused by *Escherichia coli*. In many, the inflammation is necrotizing and is associated with thrombophlebitis of the peripelvic veins. Pneumaturia, the result of the action of the colon bacilli and other bacilli on the sugar in the urine, is common (Harrison and Bailey). Some examples of cystitis emphysematosa (Levin), and of an emphysema-

most frequently caused by the staphylococcus (Simeone).

Relation of Renal Disease to Hypertension

In 10 to 15 per cent of the population, both systolic and diastolic blood pressures increase with age to above 140 systolic and 90 diastolic. The blood pressure of the rest of the population remains fairly constant from young adulthood to old age. The medical services of life insurance companies have determined conclusively that the life expectancy for any person with a pressure above 140/90 is considerably less than that for a person with a lower pressure. It must be concluded that any persistent increase of the blood pressure above 140/90 should be regarded as pathologic and designated as "hypertension" (Robinson and Brucer).

Hypertension in Man and Experimental Animals. It should be emphasized that hypertension is a symptom and not a disease. When found in a patient, every effort should be made to determine the nature of the underlying condition responsible for the elevation in pressure.

General Types of Hypertension. Hypertension in man may be conveniently divided into acute, transient, and chronic. Acute hypertension is the increase of blood pressure during exercise and under emotional strain. It is probably directly related to physiologic alteration in the heart and blood vessels. Transient hypertension is a phenomenon noted particularly as a part of the menopausal syndrome. The blood pressure varies from hour to hour and from day to day, by as much as 40 to 50 mm. By "chronic hypertension" is meant a condition in which the blood pressure day after day, month after month, and year after year, remains consistently above 140/90. A certain number of cases are associated with increase of intracranial pressure, caused by tumor, hemorrhage, or any other space-consuming lesion within the cranial cavity. The increase of blood pressure is probably caused by anemia of the vasomotor center in the medulla (Meyer). An occasional instance is observed in association with a tumor of the adrenal gland, usually of the medulla, most often a pheochromocytoma. Since the original observations of Richard Bright on the association of renal disease with hypertrophy of the heart, the close correlation of various types of disease of the kidney with an elevation of blood pressure has been known.

Early Studies on the Cause of Hypertension. Following the demonstration of the relation of the kidney to hypertension, pathologists undertook to study the problem in animals. The most notable conclusions were that bilateral nephrectomy gives no elevation of blood pressure; that reduction in the amount of functional renal tissue occasionally gives moderate elevation; that destruction of the renal substance by x-ray consistently gives moderate elevation; that occlusion of one renal artery gives slight temporary elevation; that occlusion of both renal arteries in some animals gives moderate to severe elevation; that little or no elevation in many of these experiments follows when the renal vein is also ligated; and that permanent obstruction of the ureter gives an elevation (Goldblatt).

The Experiments of Goldblatt. These general conclusions were not crystallized until Harry Goldblatt reasoned that all of them pointed to one conclusion: that the kidney must remain in the body, and that it must be partially deprived of its blood supply. He placed a small clamp on one renal artery of dogs and monkeys, and produced within a few days an elevation of blood pressure, which returned to normal in about one month. When clamps were applied to both renal arteries a permanent hypertension resulted, and was maintained for periods up to nine years in dogs. Except terminally, there was no real insufficiency.

Further studies to elucidate the mechanism of hypertension following renal ischemia have revealed several controlling factors. Destruction of the nerve supply to the kidney, removal of the sympathetic ganglia and nerves about the kidney, and destruction of the spinal cord have no influence. The condition is therefore not neurogenic. Similar clamping of other arteries of the body does not change the blood pressure. Clamping of a femoral artery that supplies a transplanted kidney results in hypertension. Removal of all endocrine glands except the pituitary and the adrenal has no influence. In established hypertension, removal of the pituitary results in a lowering of the pressure. Adrenalectomy inhibits the appearance of hypertension, unless cortical substitutional therapy is used.

Humoral Mediation of Hypertension in Renal Ischemia. From these experiments it was logical to conclude that the ischemic kidney elaborates a pressor substance which enters the renal vein and acts on the smaller blood vessels throughout the body. But a pressor substance has been recovered not only from ischemic kidneys but normal kidneys (Williams, Grollman, and Harrison). This pressor substance is known as "renin." Renin injected into an intact animal gives a transient elevation of blood pressure, but when injected into an isolated structure, such as a rabbit's ear, there is no elevation of the blood pressure. If normal blood is added to the renin, there is an increase of pressure, but this increase cannot be secured in the same or another ear with the same fluid. It follows, then, that normal blood contains a substance known as "renin-activator" that is used up in the process of inducing hypertension. The end

product of the interaction of renin and renin-activator is a crystalline substance known as "angiotonin." Injection of angiotonin into an intact animal or perfusion through a part of an animal gives a prompt, temporary increase of pressure. However, injection into nephrectomized animals and into animals with ischemic kidneys gives a greater response than injection into normal animals. It follows then that the serum of a normal animal contains a substance that inhibits the action of angiotonin, and that this substance is produced by the kidney. It is known as "angiotonin-in-

Pathologic Anatomy of Hypertension. Although the attention of the pathologist is focused on the kidney, the condition known as "essential hypertension," or, as proposed in the foregoing, "primary renal hypertension," produces changes throughout most of the organs of the body. It is commoner in men in a ratio of about 3:2 and is rarely observed in persons under forty. The larger blood vessels, including the aorta, show a variable degree of arteriosclerosis. The heart is increased in size and weight, and averages about 550 gm. The cavities are dilated, but there is no

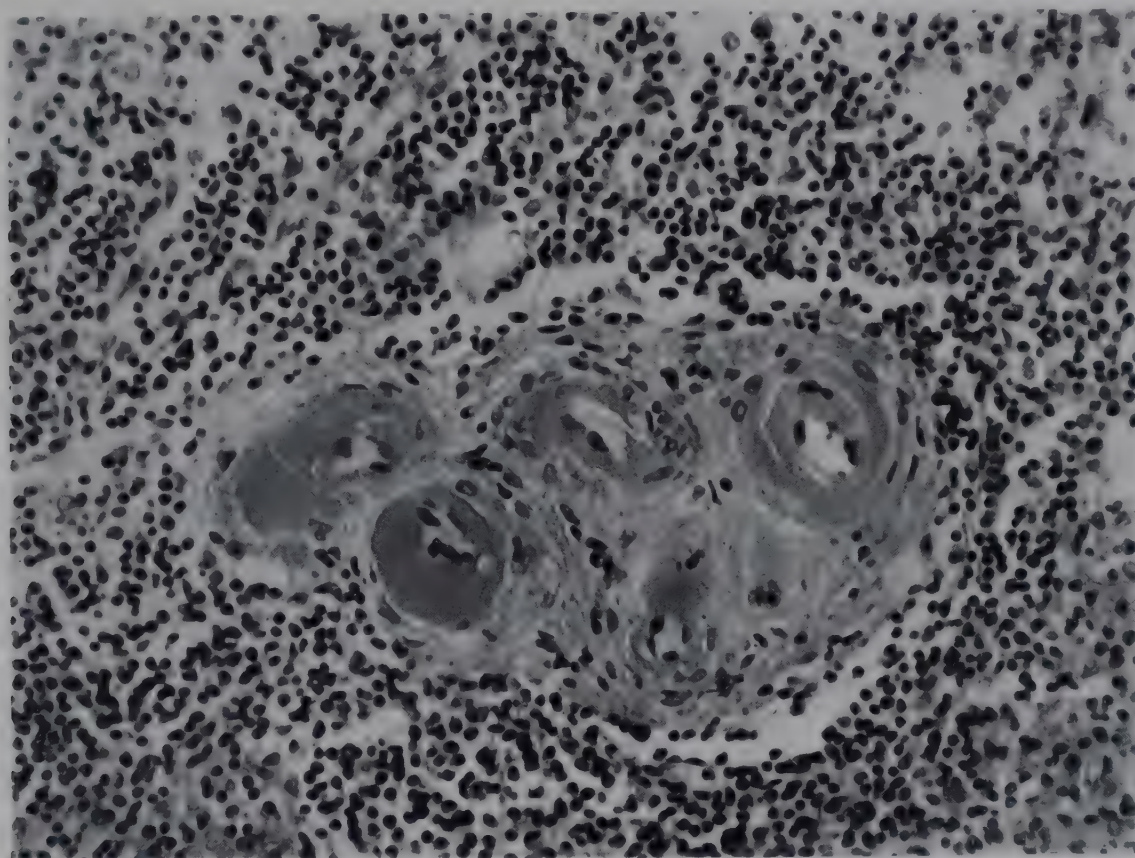


Fig. 368. Arteriolosclerosis in spleen.

hibitor." A similar inhibitor for renin can also be demonstrated. If a solution of angiotonin in blood is repeatedly used, it gradually loses its effect; and if new blood is added, the effect is again restored to the high level. Thus there must be some substance in blood that is necessary for the action of angiotonin, known as "angiotonin-activator" (Page and Helmer).

Terminology of Hypertension in Man. The most satisfactory classification of chronic hypertension recognizes two types, renal and extrarenal. The extrarenal types include those caused by disease of the brain and of the adrenal gland, and occasional rarer types. Any disease of the kidney may at times be associated with hypertension, but one of three is observed in almost all patients: glomerulonephritis, arteriolar nephrosclerosis, or chronic pyelonephritis.

disease of the valves. The coronary arteries show a variable degree of arteriosclerosis, and in a significant number there is thrombosis of the artery with infarction of the myocardium. The cerebral arteries are the seat of moderate to severe arteriosclerosis, and in some patients there is hemorrhage into the cerebral substance. Throughout the body there is some thickening of the arterioles, with fibrosis of the tissues, particularly of the pancreas and of the myocardium (Moritz and Oldt). In some instances there are small foci of hyperplasia of the adrenal cortex (Rinehart, Williams, and Cappeller).

Thus essential hypertension is a disease of the small blood vessels of all of the tissues and organs of the body (Foa, Foa, and Peet). This restriction of blood supply, followed by degeneration of parenchyma and fibrosis, leads

to gradual failure of certain organs, notably the kidney, the heart, and the brain. With failure of the kidney there is uremia; with failure of the heart, cardiac failure or infarction, and with failure of the brain, atrophy and hemorrhage. Of all patients with hypertension, about 60 per cent die of cardiac failure or infarction of the heart, 20 per cent of cerebral hemorrhage, 10 per cent of renal insufficiency, and 10 per cent of miscellaneous lesions and conditions (Bell and Clawson).

Physiologic Considerations. The formation of urine is the result of the simultaneous occurrence of three processes: (1) glomerular filtration, or the passage of a colloid-free filtrate of blood plasma through the glomerular capillary endothelium and the capsular epithelium as the result of an excess of hydrostatic over colloidal osmotic pressure; (2) tubular excretion, or the passage of solutes from the plasma in the peritubular capillaries through the cells of the proximal convolution of the tubule to its lumen; and (3) tubular resorption, or the partial removal of solutes and water from the lumen of the distal half of the tubule by the cells. There are available for this purpose about a million individual nephrons in each kidney. A nephron consists of a glomerulus and a tubule averaging about 33 mm. in length (Edwards).

Renal Blood Flow in Patients with Hypertension. As is suggested by these experimental observations, patients with advanced hypertension show a striking reduction in the rate of renal blood flow and reduction in the total tubular mass. However, in patients with slight to moderate hypertension, the values are within the lower levels of the normal range. In some patients there is no demonstrable change in renal blood flow. Whether the renal ischemia is primary or secondary must remain for future investigation to determine (Friedman, Selzer, and Rosenblum; Goldring, Chasis, Ranges, and Smith; Findley, Edwards, Clinton and White).

Capacity of the Renal Vascular Bed at Autopsy. In a similar way it is possible to demonstrate at autopsy by perfusion methods that there is a reduction in the rate of renal circulation in advanced cases; but with mild cases it is not apparent (Cox and Dock).

Postural Hypertension. An interesting confirmation of the experiments of Goldblatt is given by the phenomenon of postural hyper-

tension in man. When patients with this rare condition stand erect, the kidney falls downward and pinches on its own blood supply. It can be demonstrated that these persons have a reduction in renal blood flow that disappears in the prone position, as does the hypertension (McCann).

Idiopathic Hypertension. Spasm of Arterioles. Despite the increasing evidence that has accumulated in the last decade incriminating the kidney in most cases of hypertension, there still remain a significant number of cases in which all anatomic, physiologic, and chemical methods fail to demonstrate any of the postulated conditions for primary renal hypertension. These may represent spasm of arterioles without anatomic change in the vessels (Castleman and Smithwick).

Clinicopathologic Correlation in Renal Insufficiency

Our knowledge of the function of the kidney is so extensive and so complex, and the correlation of anatomic and function changes so incomplete, that it is not possible to give a full discussion in a general textbook. The reader should consult the excellent papers of Van Slyke and his colleagues, Addis, Peters, Russell, and others. In bridging the gap from clinical manifestation to anatomic change, the following list may be helpful.

Polyuria:

Increased rate of glomerular filtration or decreased rate of tubular resorption or both, usually related to slight glomerular and tubular degenerative changes

Oliguria, anuria:

Decreased rate of glomerular filtration or increased rate of tubular resorption or both, usually related to advanced damage to glomeruli or tubules

Hematuria:

Severe damage of glomerular capillaries by inflammation (glomerulonephritis) or by ischemia (malignant nephrosclerosis)

Proteinuria:

Increased permeability of glomerular capillaries, induced by inflammatory or degenerative changes

Cylindruria:

Degenerative changes in the tubules and inspissation of protein in the tubular lumina

Retention of Nitrogenous Substances:

A measure of the intact functioning glomeruli or the effective renal blood flow or both

Edema:

A disturbance of the metabolism of water seen (1) in degenerative lesions, especially lipid nephrosis, (2) in the initial stages of acute glomerulonephritis, and (3) in cardiac failure of terminal stages of all forms of Bright's disease

Hypertension:

A sign of circulatory changes, and if high and prolonged is associated with thickening of arterioles

Uremia is a clinical syndrome which occurs in conjunction with and as the result of the retention in the blood of urinary waste products. It is seen in all types of renal disease in which there is renal insufficiency, including acute and chronic nephritis, advanced arteriolar nephrosclerosis, and acute and chronic pyelonephritis. It should not be confused with the syndrome of pseudo-uremia, characterized by headache, convulsions, and signs of increased intracranial pressure, resulting from edema of the brain alone; or with cerebral manifestations resulting from an independent disease of the cerebral blood vessels.

Pathologic Anatomy. The pathologic findings in uremia depends on two factors: the basic disease responsible for renal insufficiency, and the lesions which are an integral part of the uremic complex. Only the latter will be discussed here. The brain is edematous and increased in weight. The convolutions are flattened and the sulci narrowed. The brain substance is of decreased consistency. The microscopic picture is characteristic of edema of the brain. Serofibrinous inflammation of serous membranes, most commonly of the pericardium and less commonly of the pleura and peritoneum, is one of the characteristic findings. In the stomach, small intestine, and large intestine, the mucous membrane is swollen, velvety, and hyperemic. The pancreatic acini are dilated and filled with inspissated secretion (Baggenstoss). Throughout the body, in the skin, in the mucous membranes, in the pelvis of the kidney, and in the serous membranes, there are numerous petechiae and ecchymoses. On the surface of the skin, particularly over the forehead, fine white crystals of urea and uric acid may be seen.

Chemical Alterations in Uremia. *Acid-Base Balance.* Acidosis results from the following: a loss of base and of chlorides in the urine (when there is polyuria) and in the vomitus; the failure of the mechanism for the formation of ammonia; and the retention by the diseased

kidney of sulfates, phosphates, and organic acids. This acidosis is frequently associated with an excessive loss of fluid as well, so that there is dehydration.

Chlorides. The chlorides in the body fluids are reduced both absolutely and relatively. Occasionally, there is retention of chlorides. In animals a decrease in the concentration of chlorides in the blood and spinal fluid results in weakness, stupor, and coma.

Magnesium. There is probably a slight increase of magnesium in most instances of uremia. It is unlikely that this alteration is clinically significant.

Potassium. The potassium concentration in the blood is elevated in renal insufficiency, and in some patients may produce damage to the myocardium, seen as changes in the electrocardiogram (Keith and Burchell).

Calcium and Phosphorus. The calcium of the serum is decreased largely at the expense of the ionized fraction. There is an additional loss if there is a depletion of the plasma proteins as well, since a part of the serum calcium is bound to protein. The reason for this change in calcium may be attributed to a number of factors: the retention by the diseased kidney of phosphorus, with the normal physiologic reaction to maintain the calcium-phosphorus ratio; and the retention of oxalate and citrate by the kidney, and union of these anions with the ionized calcium, and conversion to an un-ionized state.

Phenols. Available methods indicate that there is a significant retention of phenolic compounds. Comparison with physiologic experiments in animals indicates that many of the phenomena, particularly those referable to the central nervous system, result from this increase of phenolic compounds.

Guanidine. This is increased in some instances of uremia, and it is possible that some or all of the muscular twitching is referable to this substance.

Urea. One of the most characteristic features of uremia is the increase in the urea of the blood, but it is equally clear that there is no correlation between the height of the blood urea and the severity of the symptoms. Hence it is unlikely that the simple retention of urea is responsible for any of the signs and symptoms. The urea in the intestinal canal is converted by bacteria into ammonia, and at autopsy the odor of ammonia is demonstrable,

particularly in the cecum. It is possible that this increased quantity of ammonia is responsible for the catarrhal, at times hemorrhagic, gastro-enterocolitis.

Uric Acid and Creatinine. In advanced uremia there is retention of both of these substances, but there is no evidence that they play a part in the pathogenesis of uremia.

Physiologic Basis of the Clinical and Anatomic Manifestations of Uremia. *Coma.* The clinical manifestation, coma, is probably related to the increase of aromatic phenols and the decrease of chlorides, and possibly to the increase of magnesium.

Increase in Neuromuscular Irritability. The decrease in ionized calcium, especially in the cerebrospinal fluid, is the mechanism for the increase in irritability, expressed clinically by muscular twitchings, extensor rigidity, and chronic spasmodic jerks of the muscles of the extremities. Convulsions are extremely rare in uremia.

Changes in the Circulatory System. The mechanism of production of the fibrinous pericarditis is unknown. In about one-half of the cases a pyogenic coccus can be cultured, while in the other half there is no demonstrable bacterial cause. It has been suggested that the increased phosphorus may play a role. The increase in blood pressure is probably based on changes in the electrolytes of the cerebrospinal fluid.

Disturbances in the Gastro-intestinal Tract. The vomiting so characteristic of uremia may be of central or peripheral origin. A central cause is cerebral edema with increase of intracranial pressure, and a peripheral cause is the increase of ammonia and guanidine in the stomach.

Anemia. The anemia of chronic renal disease and of uremia is difficult to explain. It is certainly not caused by the inconsequential loss of blood in the urine. It is known that phenolic compounds damage the bone marrow, and this serves as the best explanation at the present time.

Manifestations in the Skin. The purpura has never been adequately explained. The decrease in ionized calcium seems an unlikely cause. It is known that there is material damage to the liver in uremia, and hypoprothrombinemia is a more probable cause. The yellow pallor of the skin is caused by oxidation of retained urinary chromogens. The

pathognomonic but rare manifestation of uremic "frost" is an indication of the extremely high values of urea in the sweat. An explanation of the pruritus is not apparent.

Prerenal Azotemia. By this term is meant an overloading of the body fluids with the end products of protein metabolism in the presence of functional integrity of the kidneys. It is seen in connection with massive hemorrhage in the gastro-intestinal tract and under other rare conditions, such as adrenal insufficiency (Becher, Harrison and Mason).

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LXXXVIII

Congestive Cardiac Failure

Congestive cardiac failure is that clinical condition in which the myocardium is unable to maintain an adequate flow of blood to all tissues of the body. It should be distinguished from circulatory failure in which the myocardium is adequate, but there are other factors such as shock or hemorrhage that lead to insufficient flow of blood (Harrison).

of water and salt, which in turn induces increase in blood volume, edema, and elevated venous pressure.

The careful clinical and chemical investigations of Harrison, Starr, and Warren and Stead indicate that the first detectable change in congestive cardiac failure is retention of salt and water. Hence, it appears that the

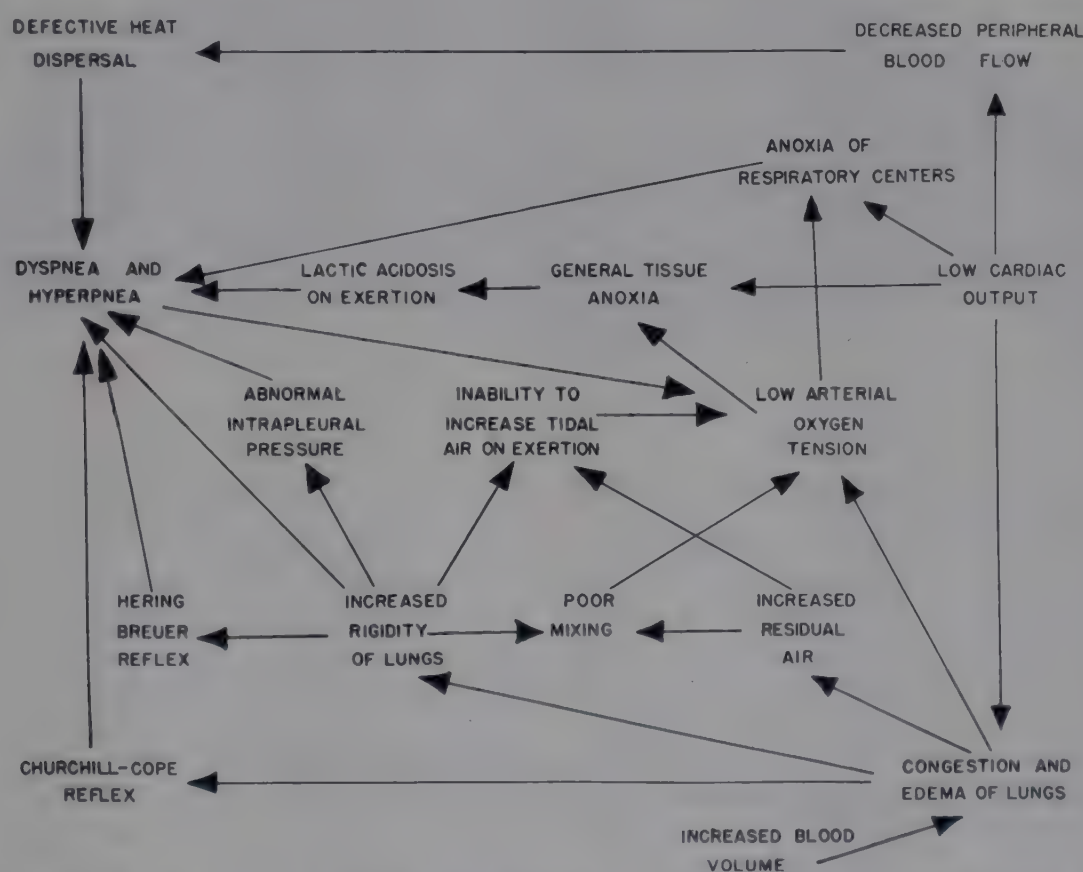


Fig. 369. Interrelations of the causal factors in dyspnea. (Modified by Altschule from a diagram originally published by him in *Medicine*, Vol. 17, Williams & Wilkins Co.)

Forward and Backward Failure. There are two theories of the mechanism of congestive cardiac failure. The theory of backward failure postulates that the inability of the failing myocardium to accept the venous blood results in an increase of venous pressure and thence the signs of decreased flow. The theory of forward failure states that the primary change is inadequate cardiac output. The resultant decreased flow in the kidney leads to retention

edema precedes the increase of venous pressure and the theory of backward failure is therefore not valid.

Anatomic Changes in the Lungs. The lungs are enlarged, firmer than normal, and dark red, and a large quantity of blood seeps from the cut surface. This is the picture of acute passive hyperemia of the lungs. It proceeds to hemorrhage and phagocytosis of the extravasated erythrocytes by mononuclear cells.

Gradually, the color changes to a rusty brown, and at the same time there is proliferation of fibroblasts with increased firmness and decreased elasticity of the pulmonary tissue—brown induration of the lungs—and chronic passive hyperemia.

Physiologic Sequelae. The dilated blood vessels take up space that would normally be occupied by air. Further, the rich vascular network and the fibrosis impair the elasticity of the lung. Hence there is a decrease in the total pulmonary volume, complemental air, and reserve air, and an increase of residual air. The decreased vital capacity and the decreased rate of flow of blood result in a significant fall in the oxygen-saturation of the arterial blood. Both of these changes are responsible

filled with blood. As the hyperemic central regions increase in size, they become confluent and isolate the hepatic parenchyma about the portal canals. There is pressure atrophy of the hepatic cords between the dilated sinuses. The liver in chronic passive congestion has a mottled surface composed of a continuous red matrix enclosing isolated brownish yellow foci. If there is in addition a fatty degeneration of the periportal parenchyma, the mottled yellow-red is such as to remind some of a nutmeg, hence “nutmeg liver.” In longstanding cases, or in advanced stages, there are proliferation of fibrous tissue in the central zone, and the production of congestive cirrhosis (Garvin). Some think that central necrosis is not the direct result of passive hyperemia, but

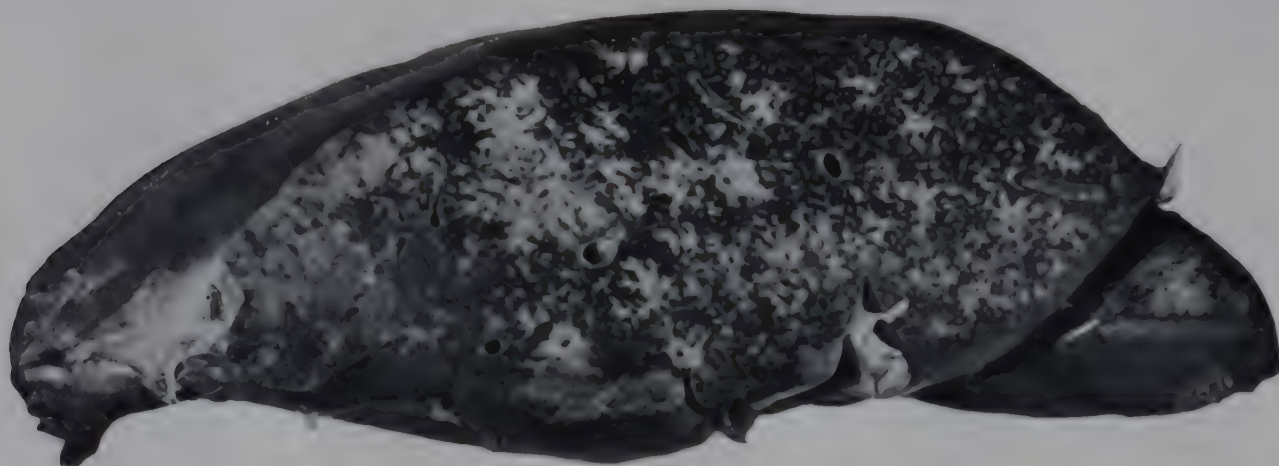


Fig. 370. Chronic passive congestion of liver.

for the clinical symptoms: hyperpnea and dyspnea (Altschule, Zamcheck, and Iglauer). The many other factors that contribute to dyspnea are summarized in Fig. 369, taken from the paper of Altschule. The increase in pulmonary size in turn leads to an increase of intrapleural pressure (decrease of negative pressure) that interferes with the return flow of blood in the peripheral veins. The hemorrhage and the presence of hemosiderin in the smaller bronchi are occasionally reflected in a rust-colored sputum.

Anatomic Changes in the Systemic Circulation. The increase of blood volume and of venous pressure and the presence of edema lead to a series of changes in most of the tissues of the body.

Liver. As the hepatic veins and their radicles, the central veins of the liver, dilate, the liver enlarges and extends below the costal border. The capsule is stretched, and there may be slight pain. The sinusoids, especially in the central zones, are greatly dilated and

is caused by an additional factor of toxic damage from bacterial or chemical substances elaborated in other parts of the body.

Functional disturbances based on the anatomic alterations in the liver are slight and inconspicuous. Hyperbilirubinemia, even to the point of clinical jaundice, is occasionally present, presumably caused by an impairment of the excretory ability of the hepatic cells by anoxia. Decreased values of other liver function tests are rarely observed.

Spleen. The spleen is moderately enlarged, and weighs from 300 to 500 gm. The capsule is slightly thickened, and the splenic substance firm and dark purple. The malpighian bodies are indistinct. The sinusoids are dilated, and are lined by prominent cuboidal cells. The pulp cords contain an increased amount of fibrous tissue. Within splenocytes in all part of the pulp there are active erythrophagocytosis and slight hemosiderosis.

Pancreas. The pancreas is firm and grayish pink. Few changes are seen microscopically

except for a rather distinctive type of interlobular fibrosis. Fibroblasts are prominent, and each lobule is partially or completely isolated.

Gastro-intestinal Tract. Throughout, the wall of the gastro-intestinal tract is thickened through the accumulation of fluid, especially in the submucosa. In the stomach the mucosa is thickened and dark red, and covered by a thick, viscid mucus. The edema of the submucosa is best demonstrated in the cecum. The mucosa is redundant, and can be easily lifted from the underlying tissues. The hyperemia of the wall of the intestine causes lack of tonus, diminution of peristalsis and emptying time, and decrease in specific secretions. These in turn lead to anorexia, nausea, distention, gaseous eructations, and flatulence.

Kidneys. The kidneys are slightly enlarged and dark red, and on section a quantity of blood oozes from the surface. The pyramids are dark purple in contrast with a lighter red cortex. The glomerular capillaries and the peritubular capillaries are dilated and filled with red cells. The tubular epithelium shows varying degrees of degenerative change, usually only slight. In the remainder of the urinary and genital tract there are few if any distinctive alterations resulting from chronic passive hyperemia. The inadequate circulation through the kidneys leads to poor renal function, recognized by a high specific gravity of the urine, albuminuria, an elevation of the blood nonprotein nitrogen to not more than 50 to 60 mg. per 100 cc., and a depression of urea clearance.

Extremities. The most obvious anatomic change in the extremities is the edema. In all of the interstitial space and within the cells there is an increased amount of fluid. When the tissue is cut, a limpid, clear fluid exudes from the tissues. The application of pressure in the living patient produces a deformity of the tissues known as "pitting edema."

There are few functional alterations of the peripheral tissues, but in severe failure creatinuria may appear, indicative of anoxemia of the muscles. The well known muscular weakness in cardiac failure may be related to this defect of metabolism.

General Chemical and Physiologic Changes. The alveolar carbon dioxide and the arterial and venous carbon dioxide content or tension are lowered. The oxygen saturation of arterial blood may be decreased to 88 per cent. The blood and urinary lactic acid is increased, especially after exercise. As would be expected from the anatomic observation of dilated venous channels, there is a significant elevation of venous pressure and of the pressure of the cerebrospinal fluid. The protein content of the transudates varies from 0.6 to 1 per cent and the specific gravity of the fluid is usually less than 1.012.

The slight elevation of body temperature is probably related to the poor dispersal of heat by the sluggish circulation. The fever, plus the muscular effort of dyspnea, is the cause of the increased basal metabolic rate.

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LXXXIX

Miscellaneous Diseases of the Cardiovascular System

In addition to the four definite types of cardiovascular disease considered in preceding chapters—congenital, rheumatic, syphilitic, and hypertensive—there are many isolated lesions and diseases of the heart and blood vessels. It is not feasible to discuss all of them here. The reader should consult the larger books on cardiology for details.

Effects of Increased Intrapericardial Pressure

Under normal conditions of respiration, the blood returning to the heart meets no obstruction at the point where the venae cavae pass into the pericardium. Under pathologic conditions the pressure in the pericardial sac may be increased and may compress the short segments of the caval vessels within the pericardial cavity.

Acute Increase. An acute increase of pericardial pressure is usually caused by hemorrhage from wounds of the heart or coronary arteries, from rupture of an infarct of the heart, or from intrapericardial rupture of a dissecting or saccular aneurysm. The caval veins are compressed and a diminished amount of blood is returned to the heart. The large venous channels dilate, and the vaso-motor reflexes maintain the blood pressure up to a point of a 50 per cent diminished output. If the homeostatic mechanisms are exceeded, there is a failure of arterial circulation; the skin becomes moist, cold, and pale; and there is a period of excitement and anxiety followed by a loss of consciousness, resulting from anoxemia of the brain. Cardiac sounds are distant or inaudible.

Chronic Increase. The physiologic changes of a chronic increase of intrapericardial pressure usually result from a longstanding accumulation of fluid, or from dense fibrous adhe-

sions that constrict the atria—chronic constrictive pericarditis (Burwell and Ayer; Blacklock and Burwell). The causes of chronic constrictive pericarditis are tuberculosis and healed acute pericarditis in half of the cases, and unknown in the other half (Paul, Castleman, and White). The venous pressure may increase to 30 or 40 cm. of water. There is dilatation of all venous channels; the liver and spleen enlarge; and there is transudation of fluid into the serous cavities. The systolic and the pulse pressures are reduced, and cyanosis, weakness, and dyspnea on exertion are present. The minute-volume output of the heart is reduced, and the vital capacity is diminished (Beck and Cushing).

Focal Fibrous Thickening of the Pericardium. Fibrous thickening of the pericardium, fibrous obliteration of the pericardial sac, and calcification are observed after suppurative inflammations, in patients with rheumatic heart disease, and in association with organizing or healed infarcts. In addition, small foci, 1 to 3 cm. in diameter, are seen at autopsy, in which the pericardium is thickened, grayish white and opaque. These are known colloquially as “milk spots” or “soldier spots.” They are composed of a dense connective tissue, infiltrated with a few lymphocytes. They are uncommon in childhood, but after the age of thirty-five are found in 35 to 50 per cent of all hearts (Nelson).

Hypertrophy and Dilatation of the Heart

It should be emphasized that hypertrophy and dilatation of the heart is not a disease, but only an anatomic lesion.

Weight of the Normal Heart. The heart weighs at birth from 20 to 25 gm. and forms 0.65 to 0.80 per cent of the body weight. Dur-

ing the second year the relative heart weight is about 0.5 per cent of the body weight, and this relation obtains with individual variation through the remainder of childhood and maturity (Scammon, quoted by Smith). In adults the size of the heart varies with weight, height, and age, especially weight. In the range of body weight from 54 to 94.5 kg. (99 to 208 pounds), the relation of the weight of the heart to body weight in men is 0.43 per cent and in women 0.40 per cent (Smith).

measurement of the phenomenon of a limit of hypertrophy. Thus, the relative reduction in reserve capacity of the hypertrophic heart may result from the fact that since the individual fibers have reached their maximal growth, and probably also their maximal functional strength, further hypertrophy is impossible (Karsner, Saphir, and Todd).

Physiologic Factors Inducing Hypertrophy. The mechanism of experimental hypertrophy is fairly clear. In dogs in which a stenosis of



Fig. 371. Dilatation of veins in patient with constrictive pericarditis. (Case reported by Stewart and Heuer: Arch. Int. Med., Vol. 63.) Photographs on infra-red sensitized plates.

Pathologic Anatomy. Hypertrophy may be estimated by inspection, or by determination of the weight. Dilatation similarly may be estimated by inspection, or measured by determining the greatest length between the semilunar valves and the apex of each ventricle. In hypertrophy the individual fibers are increased in breadth, and the nuclei tend to be square-ended. The studies of Karsner, Saphir, and Todd clearly show that there is no appreciable increase in the number of fibers, and that with the increase in the breadth of each fiber there is a distinct tendency towards uniformity in breadth. It is possible that this is the objective

the ascending aorta has been produced, hypertrophy results by the eightieth day. Serial studies reveal that there is first a dilatation, usually reaching a maximum on the third to the sixth day, and returning to normal by the tenth day. The observation that the hypertrophy ensues even when the stenosis of the aorta is alleviated during the period of dilatation gives definite evidence that hypertrophy is not a response to an increased demand for work, but rather is the response of muscle to injury. Histologic studies during the period of dilatation show hydropic degeneration. It is also evident that hypertrophy does not occur

without a preceding dilatation (Eyster). This explanation of hypertrophy fits well with all observations made at autopsy.

Anatomic Lesions Associated with Hypertrophy. There are two outstanding anatomic lesions associated with hypertrophy and dilatation of the heart: chronic valvular disease and renal disease with hypertension. Other rarer associations are with abnormal communications in congenital cardiac disease, with obstruction of the blood vessels of the lung, and with inflammation and degeneration of the myocardium.

Cardiac Musculature. Predominantly Unilateral Hypertrophy. The myocardium represents a group of muscles, some of which are arranged about the right ventricle, some about the left ventricle, and some of which cover both ventricles (Mall). In most instances of hypertrophy of the heart the cause is such that it would operate on one ventricle more than on the other, and one may correctly speak of "hypertrophy of the right ventricle" and "hypertrophy of the left ventricle." Thus in mitral stenosis there is a predominant hypertrophy of the right ventricle, and a normal or even at times atrophic left ventricle (Karsner, Simon, and Fujiwara). On the other hand in aortic insufficiency there is advanced dilatation and hypertrophy of the left ventricle, with only a minimal hypertrophy of the right ventricle (Herrmann, Lewis). Microscopic studies of the fibers and individual muscles show a greater increase in the diameter of the fibers from muscles of the predominantly involved ventricle than from those of the other ventricle.

It is important to remember that the right ventricle is as thick or thicker than the left ventricle at birth, and that the left ventricle becomes the predominant ventricle only after from six to twelve months of life. In the adult an estimate of the degree of hypertrophy of each ventricle may be secured by measurement of the thickness of the myocardium. Normally for the left ventricle this is 12 mm., and for the right ventricle 3 mm. The myocardium of the normal atria should not exceed 1.5 mm. in thickness.

Clinicopathologic Correlation. The increase in the size of the heart may be determined by percussion or by x-ray. In the latter case with films made under known conditions, the size of the cardiac silhouette may be estimated

from a formula that takes into consideration age, height, and weight (Hodges and Eyster). More accurate evaluation of the cardiac silhouette in both the anteroposterior and the oblique positions, with demonstration of each cavity of the heart, may be used to give a clue to the causes of the hypertrophy (Eyster). Finally, the electrocardiograph has been used to demonstrate preponderance of one or the other ventricle; and the correlation between the actual weight of the ventricle at autopsy and the character of the electrocardiographic tracing is accurate (Lewis).

General Considerations of Myocarditis: Isolated Myocarditis

The diagnosis of myocarditis fell into disrepute in the early part of this century because of indiscriminate use of the term for all types of unidentified heart disease. The anatomic studies of Gore and Saphir indicate that inflammatory changes in the myocardium occur in a wide variety of diseases. Further, there is evidence also that there are clinical signs and symptoms referable to the lesions. Saphir's classification is as follows:

1. Following infectious diseases
 - a. With endocarditis
 - b. Without endocarditis
2. Specific—with characteristic anatomic structure or identifiable pathogenic organisms (rheumatic fever, tuberculosis, etc.)
3. Due to chemical poisons, physical agents, or hypersensitive states
4. Isolated—unassociated with any known illness

The types covered by the first three categories are discussed in connection with the primary disease.

Acute Isolated Myocarditis. In an occasional patient at autopsy, moderate unexplained hypertrophy and dilatation of the heart are observed. In some of these cases, the interstitial tissue is edematous and infiltrated with lymphocytes and a few polymorphonuclear leukocytes. A careful study of the clinical history and of all of the other organs at autopsy fails to reveal any other focus of inflammation or infection in the body, hence the term "isolated myocarditis." Clinically, there is a long or short period of cardiac failure, and death is usually sudden and unexpected. The condition is also known as "Fiedler's myocarditis" (Saphir).

Endocardial Fibrosis

In young adults cardiac failure may be associated with fibrosis of the endocardium and myocardium without valvular or vascular disease.

The endocardium is thickened up to 1 to 2 mm. by dense fibrous tissue, especially in the left ventricle. At points throughout the ventricle there are mural thrombi. At some points the fibrosis extends into the myocardium and separates the muscle fibers. There is scant focal infiltration with lymphocytes.

The cause is unknown, but nutritional deficiency has been suggested (Smith and Furth). The lesion is different from endocardial fibroelastosis of infants (Prior and Wyatt).

Pulmonary Embolism and Infarction

Pulmonary embolism is a disease in which death is frequently sudden. A classic example is the patient who, during convalescence from a surgical operation, gets out of bed for the first time and drops dead.

Pathologic Anatomy. At autopsy three types of disease may be recognized: fatal pulmonary embolism, incidental pulmonary embolism, and pulmonary embolism with infarcts of the lung.

Fatal Pulmonary Embolism. In this condition, the main pulmonary artery and the larger branches are filled with a twisted mass of thrombus, from 20 to 30 cm. in length, intact or broken into smaller pieces. The untwisted embolus shows lines of Zahn, valve markings, and small broken branches, which may often be matched in the femoral vein with the valves and the tributary veins. In the parenchyma of the lung there is slight edema and hyperemia, and the right ventricle is dilated. Death usually occurs so rapidly that there are no secondary pathologic changes.

Incidental Pulmonary Embolism. In many autopsies, especially those on debilitated persons, the smaller branches of the pulmonary arteries are found to contain emboli. When there are only a few, it seems unlikely that these are directly related to the cause of death, while if they are abundant, blocking of the pulmonary circulation is probably a contributory cause of death. These emboli are firmly impacted in the branches of the artery, and when removed are friable and show lines of Zahn on

their surface. The lung is hyperemic and edematous.

Pulmonary Embolism with Infarct of Lung. In some instances embolism of the smaller or larger branches of the pulmonary artery is associated with the formation of an infarct of the lung. The infarct is a pyramidal region of tissue with the base on the pleural surface and the apex at the point of vascular occlusion. In the first twenty-four to forty-eight hours the area of infarction is dark red and firm, but on section blood oozes from a moist surface. After two days and up to thirty-five days, the infarct is dark red and extremely firm, and has a dry cut surface. After thirty-five days there is beginning destruction of the blood, and the central part of the infarct becomes gray or yellow. During the early stages there is hemorrhage into the alveoli, followed in a few days by clotting of the extravasated blood and necrosis of the alveolar walls. In from one to two weeks there is beginning organization about the edge of the infarct and penetration of fibroblasts and young capillaries into the dead tissue (Fig. 46, p. 82).

Over many areas of infarction there is fibrinous pleurisy which, with recovery of the patient, goes on to organization and the formation of pleural adhesions. Correlated studies of excised lungs at autopsy show a considerable number of healed infarcts, with fibrous pleural adhesions, in patients with no definite history of pulmonary embolism and infarction (Castleman).

Relation of Occlusion of Pulmonary Artery to Infarction. Some patients with occlusion of a smaller pulmonary artery develop an infarct and others do not. In most lungs in which infarction develops there is associated chronic passive hyperemia, suggesting that hyperemia of the lungs is a predisposing cause of infarction (Garsner and Ash).

Sources of the Emboli. In most fatal cases of pulmonary embolism the emboli are derived from thrombi in the femoral and popliteal veins. Smaller emboli may come from the veins of the pelvis and from larger veins about operative fields.

Incidence of Pulmonary Embolism. Thrombi in the pulmonary arteries are found in about 10 per cent of all autopsies. Following World War I there was an increase in the incidence of pulmonary embolism in Europe, but this did not occur in America. It seems probable

that the undernutrition of the European population may have had some influence on this increase. Pulmonary emboli are found as a complication in a wide variety of conditions, but a few are outstanding: cardiac failure (White), debilitation as a result of cancer or some other chronic disease, and the postoperative state.

Predisposing Factors. It is apparent that the important predisposing causes are: inactivity, especially of the muscles of the lower extremities following a surgical operation; slowing of the circulation in the lower extremities, such as occurs in cardiac failure; interference with the return circulation of the heart, such as might be brought about by distention of the abdomen and fixation of the diaphragm after a surgical operation; and traumatic injury to the veins. These are the causes of thrombosis of the larger veins of the lower extremities and therefore predisposing causes of pulmonary embolism.

Precipitating Factors. Undoubtedly many persons develop thrombi in the larger veins, but only a few of these thrombi break loose and form emboli. Movement and physical straining are important precipitating factors. In 100 patients studied by Takáts and Jesser, pulmonary embolism occurred during a bowel movement in 15, in getting in or out of a wheel chair in 6, following the morning care in 3, during or immediately after operation in 3, in association with violent nausea, after insertion of a stomach tube, and during hiccuping in one each. In 70 there was no obvious precipitating factor.

Mechanism of Death. Patients are observed at autopsy with pulmonary emboli and a history of sudden death, in whom the amount of pulmonary circulation occluded by the embolus would seem to be an inadequate cause of death. This has suggested to some that dilatation of the pulmonary artery brings about powerful stimulation of the afferent vagal fibers, with reflex constriction of the bronchi and coronary arteries, and inhibition of the heart to cause death. The success of the treatment of pulmonary embolism with atropine and papaverine supports this theory.

Clinicopathologic Correlation. The initial thrombus in a vein of a lower extremity frequently leads to slight edema (Culp). Following surgical operations death from pulmonary embolism is commonest on the sixth

to the tenth day. The interval between the initial symptom of pulmonary embolism and death is extremely variable. About 9 per cent die within ten minutes and 33 per cent in less than one hour, while another 33 per cent survive for a day or more. In patients with multiple small emboli and infarcts of the lung, there is abundant evidence at autopsy that the infarcts are formed at different times, some being several months old. The immediate clinical effect of the lodging of the embolus is pain over the thorax, dyspnea, and cyanosis. The right pulmonary artery and the branch of the right pulmonary artery to the lower lobe are the most direct and largest continuations of the main pulmonary artery, and emboli and infarcts are therefore commonest in the right lower lobe. The occlusion of the larger part of the pulmonary circuit leads to dilatation of the right ventricle, and it is probable that this is the anatomic explanation for the electrocardiographic changes, which are similar to those of coronary occlusion (Horn, Dack, and Friedberg; Durant, Ginsburg, and Roesler). The importance of pulmonary embolism may be judged from the statement that 5 per cent of all postoperative deaths on a urologic service are directly attributable to this lesion (Culp). The judicious use of anticoagulants such as heparin when thrombosis and embolism are possible has reduced the incidence and mortality.

Primary Pulmonary Arteriosclerosis

Pulmonary arteriosclerosis and arteriolo-sclerosis without evident cause constitutes a distinct clinical and anatomic entity, frequently referred to as "Ayerza's disease." The pulmonary arteries are greatly thickened, and the intima covered by numerous elevated yellow and gray plaques. The arterioles show a corresponding thickening, largely by intimal hyperplasia, but multiplication of nuclei in the media is also seen. There is great hypertrophy and dilatation of the right ventricle.

The condition is seen at any age and in both sexes. Death is usually the consequence of cardiac failure and at times is unexpected and sudden. The outstanding clinical observations are those of interference with external respiration: dyspnea, orthopnea, cyanosis, and polycythemia. The cause is unknown (Brill and Krygier).

Idiopathic Cystic Medial Necrosis. Rupture of the Aorta. Dissecting Aneurysms

Pathologic Anatomy. These three conditions are grouped together because they represent a single entity with differing degrees of pathologic change. The basis of both rupture of the aorta and dissecting aneurysms is idiopathic cystic medial necrosis.

Idiopathic Cystic Medial Necrosis. Gross changes are rarely recognized in the absence

associated arteriosclerosis and, rarely, associated syphilitic aortitis (Moritz).

Dissecting Aneurysms. In dissecting aneurysm the rupture of the aorta goes only part way through the wall, and typically the outer one-third of the media is dissected away from the inner two-thirds. The dissection may be limited to a small area or extend the entire length of the aorta. In most instances the outer wall breaks at the same or at some other point, and there is hemorrhage into the pericardial, pleural, or peritoneal cavities, into the

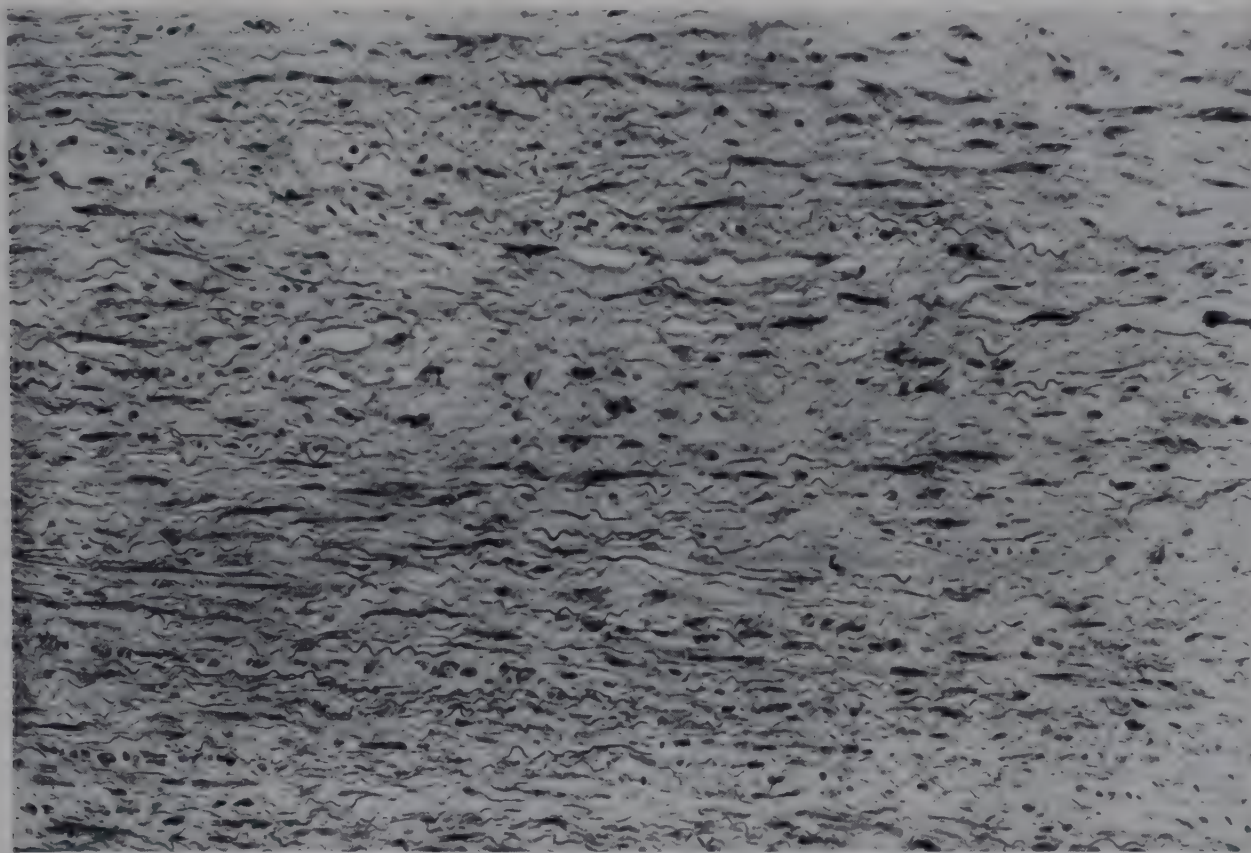


Fig. 372. Idiopathic medial necrosis of aorta. Note small cysts.

of one of the other two, but on occasion one may see small cysts or fibrosis in the cross-section of the wall of the aorta. There is deposited in the media a homogeneous, pale-staining, basophilic, acellular material between the muscle cells, and elastic fibrils. In longitudinal section the material appears to encase the elastic fibrils. It stains with most of the metachromatic dyes and shows a distinct affinity for the stains for fat (Moritz; Erdheim).

Rupture of the Aorta. In the typical example of rupture of the aorta there is a transverse tear in the first 3 cm. of the ascending aorta, 1 to 4 cm. in length. This tear extends through the entire aortic wall into the aortic reflection of the pericardium. The pericardial tissues are infiltrated with blood, and the cavity is filled. At the point of rupture and in other parts of the aorta there are the typical changes of idiopathic cystic medial necrosis. There may be

mediastinal or retroperitoneal tissues, or less commonly back into the main lumen. As the dissection becomes widespread, the smaller branches of the aorta, such as the lumbar and intercostals, are broken. Occasionally, a dissecting aneurysm may heal by thrombosis of the contained blood or by endothelization of a channel that has broken back into the original lumen. Microscopic examination reveals changes that are characteristic of idiopathic cystic medial necrosis (Tyson; McGeachy and Paullin; Shennan).

Incidence and Causal Factors. Rupture of the aorta and dissecting aneurysms are twice as common in men as in women, and are most frequent between the ages of forty-five and sixty. The causal factors are divisible into two parts: (1) the cause and nature of the primary medial disease, and (2) the factors bringing about rupture of the arterial wall. The chro-

matrophic substance characteristic of the lesion of the arteries increases with age, and might therefore be regarded as one of the manifestations of senile involution. Ischemia resulting from thickening of the vasa has been suggested as a cause (Schlichter, Amromin, and Solway). The reason for the rupture is probably to be found in an analysis of intra-arterial pressure. In most patients with rupture of the aorta or dissecting aneurysm, there is associated hypertrophy of the heart, together with nephrosclerosis, indicative of hyperten-

or into the iliac and femoral arteries. This pain is frequently followed by collapse, with vomiting, dyspnea, and loss of consciousness. Within a few hours there is usually recovery, and the signs and symptoms are then caused by the mass of blood within the aortic wall or by obstruction of the branches of the aorta. The dissection may proceed to the base of the heart and partially occlude the coronary arteries, to produce characteristic electrocardiographic changes. Dissection into the arteries of the extremities may interfere with the circula-



Fig. 373. Rupture of aorta.

sion. Most of the ruptures occur while the person is at rest or at his usual work, but some occur under conditions of physiologic hypertension, such as violent exercise or obstetrical delivery. The direction and location of the tear, that is across the ascending aorta, indicates that the bursting force is the systolic thrust of the heart. A history of an immediately preceding external trauma to the chest is rare.

Clinicopathologic Correlation. The immediate result of rupture of the aorta is the production of intense, agonizing pain beneath the sternum. This pain may radiate to the back, into the neck, or into the abdomen. Pain in the extremities is usually interpreted as extension of the dissection into the subclavian

tion, so that the extremities become cool, and the pulse cannot be felt. Dissection into the carotid arteries may lead to blindness or hemiplegia. Rupture of the smaller intercostals and lumbar branches of the aorta leads to relative ischemia of the spinal cord and paralysis. Vessels other than the aorta are rarely involved in a dissecting aneurysm (Shennan).

Temporal Arteritis

Although this disease involves principally the temporal artery, there are similar lesions in other vessels such as aorta, radial, femoral, coronary, and mesenteric arteries (Cooke, Cloake, Govan, and Colbeck).

The essential lesion is a granulomatous panarteritis with major involvement of the media. There is infiltration with lymphocytes, plasma cells, eosinophils, and rare leukocytes. Giant cells are a conspicuous feature. Necrosis and fibrosis proceed side by side indicating a low grade of chronic reaction. With lesions of the intima, thrombi form and occlude the lumen (Crosby and Wadsworth).

Inflammation about the periarterial nerves is probably responsible for the excruciating pain during active disease. Extension to the

thickened by plaques similar to those of arteriosclerosis, and in the larger aneurysms there are foci of calcification throughout the wall.

Incidence. Aneurysms are commonest about the branching of the internal carotid, the middle cerebral, and the posterior and anterior communicating arteries. Next commonest are those on the anterior cerebral artery, and then those on the branches of the middle cerebral artery. Relatively few occur on the vertebral, basilar, and posterior cere-

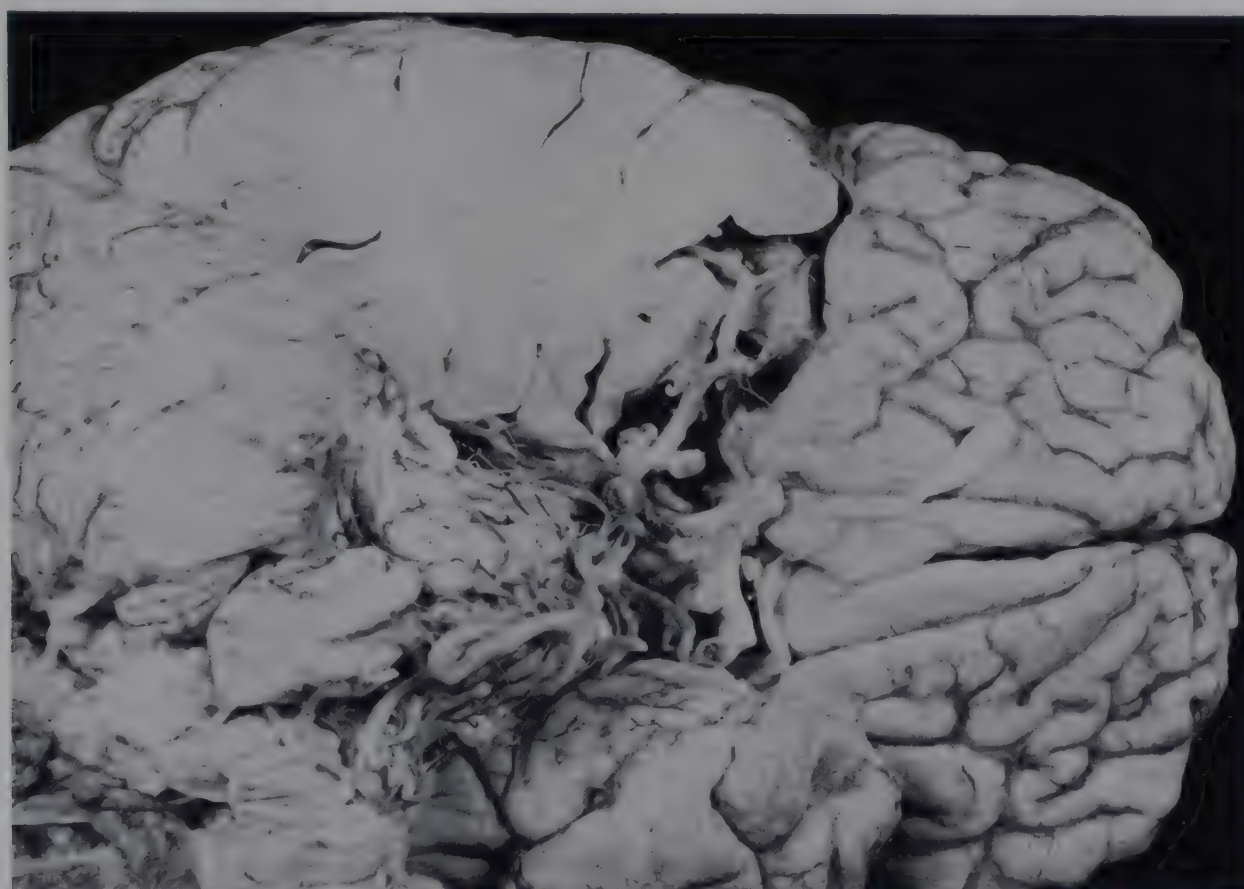


Fig. 374. Multiple aneurysms of cerebral arteries with rupture of one.

retinal artery causes blindness in one-third of the patients. The cause of this disease is unknown.

Aneurysms of the Cerebral Arteries. Subarachnoidal Hemorrhage

Pathologic Anatomy. The subarachnoidal space is filled with clotted and fluid blood from 1 to 5 mm. thick. Careful exploration by gentle washing of the blood reveals a small aneurysmal sac, 5 to 10 mm. in diameter, on one of the larger arteries at the base of the brain. The sac is formed at the point of division of two arteries, and bulges within the Y so formed. It is made up of a thin intima and the surrounding fibrous adventitia, with a complete absence of media. The intima may be

bral arteries. Aneurysms are not infrequently multiple, and are most frequent between the ages of twenty and fifty.

Pathogenesis. Syphilis is not the causal agent of this type of aneurysm and, furthermore, there is no evidence that bacteria play a role. The age distribution and the anatomic position of the sac at the branching of the arteries early led to a precise study of the histology of the cerebral arteries. It was found that in many people with or without cerebral aneurysm there is a defect in the media at this point, and that the pressure within the vessel is most effective on the coryna of the dichotomous branching. In many persons there is preexisting hypertension, as evidenced by hypertrophy of the heart, and the best theory at the moment postulates that these aneurysms

are formed by an increased arterial pressure, acting on a congenitally weak place in the arterial wall (Forbus). Support for this idea is given by the relative frequency of cerebral aneurysms and rupture of them in patients with coarctation of the aorta (Baker and Shelden).

Clinicopathologic Correlation. The effects of an aneurysm of the cerebral arteries depend

duction of the ocular fields and paralysis of the extra-ocular muscles. Rupture of the aneurysm with extensive subarachnoidal hemorrhage is marked by an abrupt onset of headache, vomiting, and loss of consciousness, all probably related to a sudden increase of intracranial pressure. The blood within the meninges effectively blocks the transmission of this pressure to the eyes, and there is rarely pa-



Fig. 375. Auriculoventricular block. (Graybiel and White.)

on the size of the aneurysmal sac and whether or not it is ruptured. Smaller aneurysms which have given no clinical symptoms are not infrequently found at autopsy. Larger aneurysms, over 1 or 2 cm. in diameter, give signs and symptoms of pressure on the brain or on the cranial nerves, depending on their location. Since the aneurysms are commonest about the internal carotid artery and its branches, the nerves most frequently pressed upon are the second and third, producing re-

pilledema. Within a short time the symptoms of irritation of the meninges follow, that is, stiffness of the neck and Kernig's sign. Lumbar puncture reveals blood within the spinal fluid, and in patients who recover, this blood disappears in from ten to thirty days. About 50 per cent recover immediately, but there is usually some residuum. About 40 per cent of the deaths occur within the first thirty minutes after the onset of headache. Instantaneous death is unusual (Richardson and Hyland).

The calcification in the wall of the aneurysmal sac or erosion of surrounding bone may be visible in the x-ray plate (Sosman and Vogt).

Disturbances in Conduction

Except for heart block, the pathologic anatomy and clinicopathologic correlation of the cardiac arrhythmias are largely unknown. The electrocardiographic diagnosis is most exact, but the pathologist rarely finds an anatomic lesion that may be logically assumed as the cause.

Some arrhythmias (premature beats, paroxysmal tachycardia) are characteristically observed in the absence of other significant disease of the heart, while others (flutter, fibrillation) are almost always associated with cardiac disease. In flutter and fibrillation inflammation or fibrosis of the atrial muscle and thrombi in the arterial appendages are frequently present. The localization of auricular, atrial nodal, or ventricular premature beats in the electrocardiographic tracing is well established, but demonstration of a morphologic change in the muscle at this point has not been made in a sufficiently large series to warrant conclusions. A short P-R interval is sometimes associated with anomalous connections between the auricle and ventricle (Wood, Wolferth, and Geckeler).

Bundle-Branch Block. Fibrosis of the myocardium and of the bundle, induced by coronary arteriosclerosis, is the most important factor in bundle-branch block (Yater, Cornell, and Claytor).

Auriculoventricular Block. The commonest lesions causing heart block are fibrosis of the muscle, fibrosis of the bundle-branches, gumma of the septum, and calcification in the septum. The fibrosis is the result of coronary arteriosclerosis, and the calcification is usually an extension from a similar lesion in the aortic valves (Yater, Cornell, and Claytor).

Congenital heart block is associated with defects of the septa and failure of development of the bundle (Yater, Leaman, and Cornell).

Tumors of the Heart

Primary Tumors. The rare primary malignant tumors of the heart are most commonly located in the base on the right side and are undifferentiated sarcomas (Whorton). Con-

genital rhabdomyoma is frequently associated with tuberous sclerosis (Farber).

Metastatic Tumors. The heart is the site of metastatic tumors in about 6 per cent of all instances of malignant neoplasms. The mode of involvement may be hematogenous, lymphogenous, or by direct extension. The site of predilection is the left ventricle. If there is pericardial effusion, it is sanguineous in only 25 per cent. The commonest sites of the primary carcinoma are the bronchus and the breast (Scott and Garvin).

Trauma to the Heart

Penetrating wounds of the thoracic wall may enter a cardiac cavity or sever a coronary artery. Hemopericardium is the result. Prompt surgical closure and ligation have saved a few patients. In fracture of ribs a spicule of bone may penetrate the heart or one of the great vessels.

Nonpenetrating trauma to the thorax may cause hemorrhage and laceration of the myocardium (Kulka). The distinction between cardiac infarct caused by occlusion of a coronary artery and a contusion of the heart is not definite. Deposits of hemosiderin in myocardial scars resulting from trauma are more abundant than in healed infarcts (Moritz and Atkins). Sudden compression of the aorta occasionally causes rupture of the aortic valve.

Physiologic Death: Carotid Sinus Reflex

Every pathologist occasionally encounters cases in which there is no adequate anatomic explanation of death. These are almost always examples of instantaneous death, in contrast with death from natural causes, such as coronary occlusion or cerebral arteriosclerosis, in which most patients live for a few hours or days. For example, a person is subjected to some great emotional strain and dies in a few seconds. At autopsy no significant pathologic changes are observed. An older person who has been in bed for some days or weeks gets up for the first time, faints, and is dead before anyone can reach him. A patient with pleural effusion is admitted to the hospital in good condition. A needle is thrust through the thoracic wall to drain off the fluid. As the needle penetrates the parietal pleura, the heart and

respiration stop, and no amount of artificial respiration or cardiac stimulation will restore life.

It is not probable that any one single explanation can be given for the cause of death in all these persons. They do, however, represent a category conveniently designated as "physiologic death." The best explanation at the present time is inhibition of the heart through a reflex mechanism. In some instances this reflex originates in the pleura, in others in the eye or nose, in others in the heart itself, in others in the higher centers of the brain, and in others, probably the majority, in the carotid sinus.

Stimulation of Nerve of Hering. At the bifurcation of the common carotid artery into the external and internal carotid arteries, there is a fusiform dilatation of the vessel. The adventitia in this region is richly innervated, and the fibers are gathered together into the nerve of Hering. Afferent stimuli through these nerves bring about a depression of blood pressure, constriction of the bronchi, constriction of the coronary arteries, and inhibition of the heart through the vagus nerve. Stimulation of the nerve of Hering by pressure induces, in normal persons, only slight changes in the circulatory system, while stimulation in persons with slight arteriosclerosis of the coronary arteries, in emotionally unstable persons, and in older persons generally, brings about more conspicuous changes and even syncope. Direct evidence that this is the mechanism of physiologic death must await further study (Weiss, Capps).

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Miscellaneous Diseases of the Urinary Tract

The close relation of the male urinary and genital tracts on the one hand, and the division of disease of the kidney into two great categories, sometimes referred to as "medical" and "surgical," render it difficult to divide the subject of genito-urinary pathology. For the sake of simplicity, however, three separate chapters have been arranged, one (LXXXVII, p. 737) on the broader aspects of Bright's disease, one (CIV, p. 924) on diseases of the male secondary sexual organs, and the present one on the diseases of the urinary system not covered in the other two.

General Effects of Obstruction of the Urinary Tract

Most lesions of the urinary tract and of the prostate are of importance and produce signs and symptoms largely because of obstruction to the onward flow of urine, or because of infection which may be the cause of or be caused by the obstruction.

General Causes of Obstruction. The urine in the urinary tract is propelled by active peristalsis, hence there are two categories of causal agents for obstruction: neurogenic and mechanical. The important neurogenic types involve the bladder, and result from lesions of the central or peripheral nervous system (p. 782). Mechanical causes may be congenital or acquired. Congenital types include anomalies of development resulting in stenosis, atresia, or valves. Acquired types include inflammations, stricture from healing of inflammation or trauma, stones, diverticula, cysts, and tumors. The obstruction may be caused by filling of the lumen or by pressure from outside.

Effects of Obstruction. An obstruction may be located in any part from the vestibule of the urethra to the secondary calices. Structures

cephalad to the obstruction are involved, and it is therefore logical to consider each part of the tract separately.

Urethra. There is little change in the urethra other than dilatation. Rarely, a diverticulum forms, or there is rupture through a weak point in the wall. In the latter instance, extravasation or a periurethral abscess follows.

Bladder. Infravesical obstruction leads to dilatation and hypertrophy of the bladder. The muscular hypertrophy follows the normal pattern of the muscle bundles so that narrow and broad trabeculae are formed. The spaces between the crossing bundles appear as small evaginations of the lumen. Occasionally, the evaginations extend beyond the wall and become true diverticula.

Participation of the trigonal muscle of the interureteral ridge, and of the muscles of Bell at the sides of the trigone in the hypertrophy, is characteristic of the response to an obstruction about the vesical neck, which interferes with the internal sphincter.

Ureter: Hydro-ureter. The effect of obstruction of the ureter is dilatation and limited hypertrophy. The dilatation affects both the cross-sectional diameter and the length. There results an elongated wide tube. Since the ureter is fixed at both ends, increase in length causes tortuosity. As the adjacent kinks, at an angle of 180 degrees, come in contact with one another, there is adventitial fibrosis, and the structure has the appearance of a valve.

The intracystic or mural part of the ureter may be held tightly by the hypertrophic vesical wall, or may dilate equally with the other parts. Inequality of dilatation of the two ureters with infravesical obstruction is frequently observed. Obstruction at the ureteropelvic junction by an anomalous vessel is one of the most frequent causes (Deming).

Kidney: Hydronephrosis. The initial effect

of an increased amount of intrapelvic pressure is an increase in size of the pelvis as a whole and blunting and rounding of the normally angulated corners of the minor calices. The latter change is more conspicuous with lesions of the upper ureter than of the lower. The pelvis gradually increases in size, and the dilating calices compress the medullary rays and papillae. The columns of Bertini are af-

vascular atrophy from a decreasing blood supply. The tubules are stretched and elongated, parallel to the surface. Some tubules atrophy and are replaced by connective tissue. The first reaction of the glomeruli is fibrous thickening of the parietal layer of Bowman's capsule. Later, there are fibrosis of the tuft and eventual formation of a fibrous ball. The intima of the arteries may be thickened.



Fig. 376. Obstruction of the urinary tract: hypertrophy of bladder, vesical calculus, hydroureter, hydronephrosis, and renal calculi.

ected last, and project into the cavity. The degree of compression of the kidney varies with the amount of dilatation inside and outside the kidney. In some persons a greater part of the pelvis is outside, and a large sac forms at the hilum—an extrarenal pelvis. The blood vessels, entering through the hilum, are stretched over the sides of the hydronephrotic sac. The renal parenchyma undergoes both pressure atrophy from the dilating sac and

Hydrodynamics. Urine is excreted through the glomeruli by a force equal to the difference in the blood pressure and the plasma osmotic pressure. It is clear that an increase of intrarenal pressure to the level of the excretory pressure would cause cessation of urinary excretion and stop the growth of a hydronephrosis. There must therefore be some mechanism for the release of the intrapelvic pressure. One clue to the mechanism of this release is given

by chemical analysis of the fluid in a hydronephrotic sac at varying periods after obstruction (Table 44).

The fact that the urinary solids do not accumulate, and the fact that there is a changing composition—decrease of urea and increase of sodium chloride—definitely indicate a constant or intermittent total resorption from the sac.

Urovenous Backflow. If a dye is put into the renal pelvis under pressure, it soon appears in the blood of the renal vein. Similarly, dye injected into a collecting tubule through a papilla is absorbed. There are thus two possible mechanisms of absorption: pyelovenous and tubulovenous. To these must be added

The type of obstruction also plays a role in determining the final result. Complete occlusion of the ureter may in some instances result in anuria and primary atrophy of the kidney, rather than hydronephrosis. Partial, progressive, temporary, or intermittent obstruction causes hydronephrosis.

An increase of venous pressure, such as would result from compression of the veins, causes an increase of excretory pressure and consequently more rapid development of hydronephrosis. Similarly, impairment of arterial supply diminishes the strength of the renal substance and hastens dilatation.

Clinicopathologic Correlation. The signs and symptoms of hydro-ureter and hydro-

TABLE 44. CHEMICAL ANALYSES OF FLUID IN HYDRONEPHROSIS (AFTER HINMAN)

Duration of Obstruction (Days)	Content of Sac (Cc.)	Concentration (Gm. per 1000 Cc.)		
		Urea	NaCl	Glucose
5.....	8	9.43	—	0.11
12.....	52	8.10	4.10	0.44
14.....	45	5.43	10.41	0.34
29.....	130	3.30	6.84	0.21
49.....	200	6.20	5.43	0.17
77.....	450+	3.75	6.48	0.30

the less easily demonstrated possibilities of pyelolymphatic and tubulolymphatic. Whether the absorption is through the vital activity of cells, by osmotic forces, or by direct rupture of the urinary lumen into a vein or lymphatic cannot be stated with certainty. It is also probable that absorption from rupture into the interstitial tissue occurs.

The relative importance of the various types of urovenous and urolymphatic backflow varies with the duration of obstruction. Early, the pressure on the papillae probably occludes the tubules, and most absorption is from the pelvis, while late the papillae are stretched and tubular absorption becomes effective.

Relation to Type of Obstruction and Other Factors. From the observations presented in the preceding paragraphs it follows that the development and rate of growth in hydronephrosis depend on a balance between intrapelvic and renal excretory pressure. When the former is higher, absorption is dominant, and when the latter is higher, excretion and increase of size are dominant.

nephrosis are largely those of the primary disease causing the obstruction. The dilatation may cause pain, but many patients have few or no complaints.

Relation of Obstruction to Infection. Infravesical obstruction frequently leads to retention of urine, inability to empty the bladder completely (residual urine), and the use of a catheter. Sooner or later, bacteria are introduced and cystitis is established. Supravesical obstruction so changes the response of the kidney to bacteria brought by the blood that pyelonephritis is the result (see full discussion, p. 750). The obstructed segment becomes infected, and the two lesions then go hand in hand—the obstruction-infection syndrome.

The hydronephrotic sac filled with pus is designated as “pyonephrosis.”

Urinary Lithiasis

A logical sequence to the preceding consideration of the effects of obstruction of the

urinary tract is a discussion of urinary lithiasis. Stones may occur in any part of the urinary tract, and they are a frequent cause of obstruction.

Pathologic Anatomy. The only completely satisfactory method for the identification of the chemical composition of a stone is by analysis, but the physician should recognize some of the gross characteristics of each type (McIntosh and Salter).

Composition. The principal components are urates, oxalates, phosphates, and carbonates of calcium, with smaller amounts of mag-

bonate and oxalate and ammoniomagnesium phosphate. Internal structure is usually amorphous.

Internal Structure. The components may be deposited as a uniform crystalline mass or in concentric layers. In the latter instance the layers may differ in composition, and the central nidus is apt to be made from substances different from the outer layers. The framework on which the crystals are held together is protein in nature.

Primary Location. Most stones are originally formed in the kidney. Primary stones

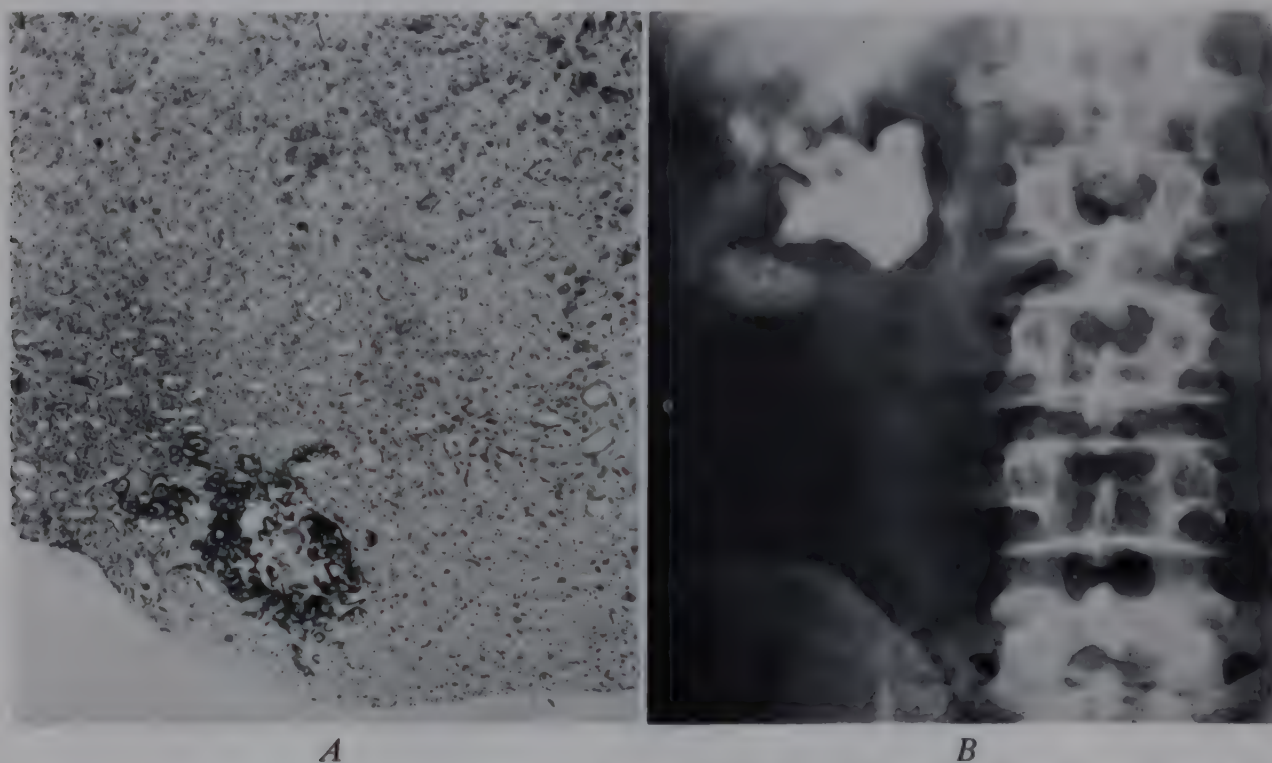


Fig. 377. *A*, Calcification in tip of renal pyramid. *B*, Calculus in renal pelvis. (Radiograph by courtesy of Dr. Sherwood Moore.)

nesium and ammonium. Uric acid may be bound or unbound. Other substances include cystine, xanthine, cholesterol, and leucine. In England half of the stones are composed largely of one substance, while in India only a seventh are "pure."

URIC ACID AND URATE STONES. This type of stone is hard, usually ellipsoidal, and yellow or yellowish brown. The internal structure may be laminated or crystalline.

OXALATE STONES. The oxalate calculus may be irregular in shape with a rough surface, or oval and smooth. The color varies from gray to brown to black.

PHOSPHATE STONES. These are typically relatively soft, and fracture easily. The surfaces are smooth, and the stones tend to mold themselves to the cavity. The color is a light or dark gray. The calcium phosphate is mixed with smaller amounts of calcium car-

of the ureters and bladder are usually associated with obstructive lesions or foreign bodies. Renal calculi are predominantly oxalates and phosphates, while vesical calculi are usually constituted of uric acid or urates.

Pathogenesis. In the 1930's Alexander Randall, on the basis of anatomic and experimental studies, developed a most satisfactory explanation of the pathogenesis of renal calculi. He observed small plaques of a calcium salt (probably nucleate) in the subepithelial tissues of the papillae. With further development of the plaque, the surface is eroded, and a jagged mass of calcium phosphate or oxalate projects into the pelvis. This mass with a plaque tears off, and a urinary calculus is formed. Plaques are present in about 20 per cent of all kidneys, as observed at autopsy.

Incidence. Causal Factors. Age. The age incidence of urinary lithiasis in Europe and

America has changed completely in the last two centuries, but in India and China there has been no change, as illustrated in Table 45 taken from data cited by Joly. This difference is usually attributed to the general improvement in sanitation and infant feeding in Europe and America. This conclusion is strengthened by the observation that renal calculi were far less common in the children of well-to-do families in nineteenth century England—0.4 per cent of all calculi in children under sixteen as compared to 13 per cent in children of poorer families.

Geographic Location. There are several sharply limited regions of the earth where renal lithiasis is common: central Russia, Mesopo-

phate, while in man the composition varies. On the other hand, the high incidence in children in India and China, and the decreasing incidence with increasing nutritional status, cannot be ignored. Further investigation is needed.

Hyperparathyroidism. From 20 to 60 per cent of patients with primary hyperparathyroidism have renal calculi (Colby); only a few per cent of all persons with lithiasis have hyperparathyroidism. The mechanism is probably related to the increased urinary excretion of calcium and phosphorus in hyperparathyroidism.

NEPHROCALCINOSIS. In addition to calculi in hyperparathyroidism, calcium may be de-

TABLE 45. AGE INCIDENCE OF URINARY LITHIASIS

	England		India and China	
	Early 19th Century	20th Century	Late 19th Century	20th Century
First decade.....	45*	51	31.4	25
Second decade.....	24†		13.9	18
Third decade.....		31	9.2	41
Fourth decade.....	12.9			
Fifth decade.....	72.8			
Sixth decade and above.....			16	

* Birth to 14 years. † 14 to 40 years.

tamia, northwest India, and Canton, China. Proposed relations of incidence to character of the soil, amount of calcium in the drinking water, and climate are not supported by objective evidence. It is perhaps significant that in India and China vesical calculi are commonest, while in Europe and America renal calculi predominate.

Race. Stones occur most commonly in Hindus, Arabs, and Southern Chinese, and least commonly in Negroes.

Diet. Avitaminosis. Rats fed a diet deficient in vitamin A develop urinary lithiasis. Some investigators report that patients with stones have delayed regeneration of visual purple, indicative of avitaminosis A, while others are unable to demonstrate a deficiency (Jewett, Sloan, and Strong). The application of these two observations to man to support a cause-and-effect relation is fraught with difficulty: in the rat most of the stones are in the bladder, and in man in the kidney; and in the rat the stones are always calcium phos-

phated in the tubules, and lead to extensive fibrosis and contraction of the kidney. The clinical picture is similar to that of chronic glomerulonephritis. As compared to other types of hyperparathyroidism, there is no hypophosphatemia, less hypercalcinuria, increased fecal excretion of calcium, and a less elevated urinary-fecal partition of phosphorus (Albright, Baird, Cope, and Bloomberg).

Clinicopathologic Correlation. The outstanding effects of urinary calculi are obstruction and infection, which are discussed in a separate section (p. 775).

Ulceration by trauma from the stone results in hematuria, and, with impaction of a stone in the ureter, extreme pain is induced by the hyperperistalsis.

The radiographic demonstration of a stone depends on the chemical composition: uric acid and urate stones are radiolucent; calcium stones and cystine stones are radiopaque. Over 90 per cent of renal and ureteral calculi are in the latter group.

Urinary Fistulas

Establishment of a connection between the urinary tract and the outside (external fistula) or another hollow viscus (internal fistula) is seen in necrotizing inflammations, after penetrating and nonpenetrating trauma, in ulceration of the tract by a stone, and in urinary tuberculosis. Malignant tumors are rarely the cause. The fistulous tract is lined by necrotic granulation tissue.

Internal fistulas may connect with any part of the alimentary tract below the esophagus,

narrow object. The serious complications, urinary extravasation and stricture, are discussed in succeeding paragraphs.

Urinary Extravasation. If the urethral wall is torn, urine passes out into the tissue. If the urine is infected, extensive cellulitis may result. The spread of the extravasated fluid is determined by the point of rupture (Fig. 378). In rupture of the pendulous or bulbous urethra the urine is confined to the penis within Buck's fascia. A hole in the bulbomembranous urethra leads into the perineum beneath Colles' fascia in front of the inferior layers of

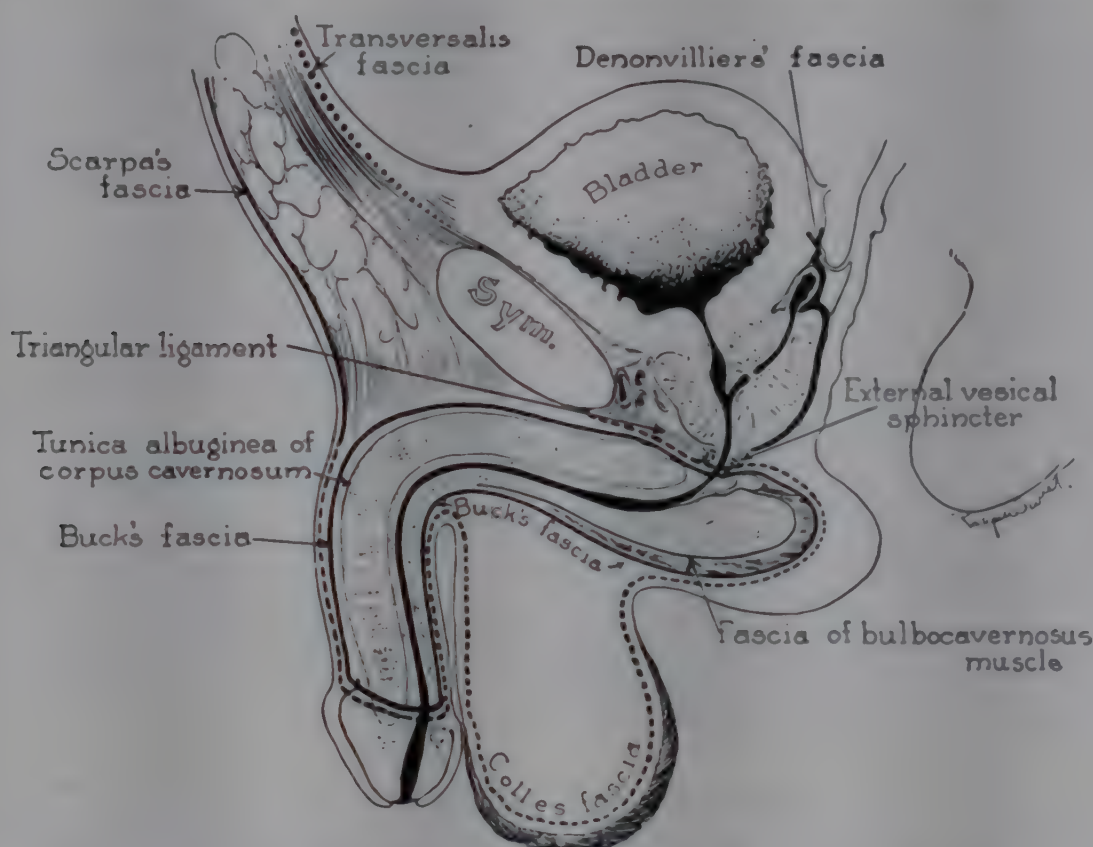


Fig. 378. Perineal fasciae and lines of urinary extravasation. (From Hinman after Wesson.)

or with the lung, thoracic duct, uterus, vagina, seminal vesicles, or vas. The urine in general is irritating to these viscera, and a chemical inflammation results. In the intestine this causes hyperperistalsis and diarrhea. Reabsorption of the excreted metabolites may give a clinical syndrome similar to that of uremia.

Diseases of the Urethra

Since the anatomic structure and the incidence of disease in the male and female urethra are different, it is best to consider them separately.

Male Urethra. Injuries. The continuity of the urethra as a closed tube may be interrupted by a penetrating wound (stab or gunshot), by unskilled instrumentation, or by nonpenetrating trauma, as in a fall astride a

the urogenital diaphragm. Secondary dissection then extends beneath the dartos of the scrotum and penis and upward over the abdomen under Scarpa's fascia. From the membranous urethra early dissection within the urogenital diaphragm usually breaks through the inferior layers and spreads as before beneath Colles' fascia. Less commonly, rupture is upward to dissect the peritoneum from the pelvic organs (Finestone).

The mortality in urinary extravasation is high, especially if associated with fracture of the pelvis (Smith and Mintz).

Stricture. CONGENITAL. Valvular folds in the urethra, just above, below, or at the verumontanum are the most frequently observed cause of congenital stenosis or atresia of the urethra. Embryologic explanations are not too clear (Lowsley and Kirwin).

ACQUIRED. Over 90 per cent of acquired strictures are the result of cicatricial contraction following gonococcal inflammation of the urethra and periurethral glands. Most of the remainder are traumatic. About three-quarters are single foci in the bulbomembranous part (Campbell).

Diverticula. What appear to be evaginations of the urethra are largely dilatation of ducts leading into the urethra, or excavations formed by calculi in the prostate or calculi impacted in the urethra.

Tumors. Any type of primary tumor of the urethra is rare. The typical malignant type is an epidermoid carcinoma of the cavernous urethra. Adenocarcinoma presumably arises in the glands of Cooper or Littre (Kretschmer). Redundant mucosa in urethritis may appear as a polyp (Graves and Guiss).

Female Urethra. Some lesion of the female urethra is the commonest cause of the most frequent urologic symptom in women—frequency and burning on urination.

Female Prostate. In about 20 per cent of all women there are irregular glands outside the urethral sheath—a true homologue of the prostate. Chronic inflammation of these is thought by some to be a cause of irritation to the vesical neck.

Inflammations. The urethral mucosa, especially near the trigone, is swollen and red. In chronic stages there are periurethral fibrosis and diffuse contraction. About the periurethral glands there is lymphocytic infiltration. Most patients give no history of either a gonococcal or nonspecific urethritis. Strictures, usually in the distal part, are most frequently secondary to gonorrhea.

Tumors. Endo-urethral carcinoma is rare and usually of the epidermoid type (Culver and Forster). A significant number of vulvar carcinomas arise about the urethral orifice (see p. 898). The urethral caruncle is discussed in another place (p. 899).

Obstructive Lesions at the Vesical Neck

In a significant number of patients with obstruction of urinary outflow similar to that seen in nodular hyperplasia of the prostate, there is no disease of the prostate. There is, however, a definite contracture of or a bar across the vesical neck which is the cause of the obstruction. Three types are recognized.

Congenital Bar. There is a hypertrophic mass of muscle extending across the trigone and partially blocking the urethra.

Inflammatory Bar. In some examples of chronic urethritis and prostatitis there is contracture of the vesical neck and partial obstruction.

True Median Bar. There are glandular and fibrous types. The glands represent hyperplasia of the subtrigonal and subcervical components of the periurethral system and project into the trigone. There may or may not be associated nodular hyperplasia of the prostate. The fibrous type is probably the result of chronic inflammation.

Inflammations and Ulcerations of the Bladder

Inflammations of the bladder may provoke a variety of characteristic reactions. In some there is diffuse or focal hyperplasia of the mucosa with the formation of redundant folds and granular projections—granular or polypoid cystitis. In some there are numerous small mucosal nodules, up to 2 mm. in diameter, composed of hyperplastic lymphoid tissue—follicular cystitis. In infections with *Escherichia coli*, especially in persons with diabetes mellitus, gas may form in the wall—emphysematous cystitis. Infections with the *Proteus* group of organisms render the urine alkaline by conversion of urea to ammonia and cause precipitation of phosphates as a crust on the inflamed mucosa—encrusted cystitis. Inflammation of an exposed vesical mucosa, as in exstrophy, may result in metaplasia of the epithelium to a mucus-secreting glandular type—glandular cystitis.

Cyst Formation in the Urinary Mucosa. In a significant number of chronic inflammations of the urinary tract, small subepithelial cysts develop—cystitis cystica, ureteritis cystica, and pyelitis cystica. The mechanism of formation seems to be central softening of solid downgrowths of the epithelium (cell nests of von Brunn). The cavity is lined by a single or double layer of cells and filled with a clear limpid or viscid fluid.

Leukoplakia in the Urinary Mucosa. Focal metaplasia to a keratinizing squamous epithelium appearing as a white, firm, opaque plaque is occasionally observed as a complication of chronic inflammation in the bladder,

ureters, and pelvis. It is a forerunner in some instances of epidermoid carcinoma.

Malacoplakia. This appears as soft, yellow, discrete or confluent nodules in the mucosa of the bladder or renal pelvis. There are edema, hyperemia, and characteristic large, epithelioid, multinucleated cells containing basophilic inclusions (Michaelis-Gutmann bodies). The cause is unknown, and most examples are in women (3:1) over forty years of age (Redewill).

Hunner's Ulcer. The lesion known as "Hunner's ulcer of the bladder" is located in the

produce pain when the bladder is distended. The cause is entirely unknown, but focal infection and pelvic inflammatory disease have been suggested. Conservative treatment has not been successful, since the ulcers are chronic (Higgins).

Dynamic Disturbances of the Bladder

Types of Adynamia. Three types of adynamia of the bladder are recognized: paralytic, cord, and atonic bladder.

Paralytic Bladder. This type is seen in lesions causing interruption of the corticospinal

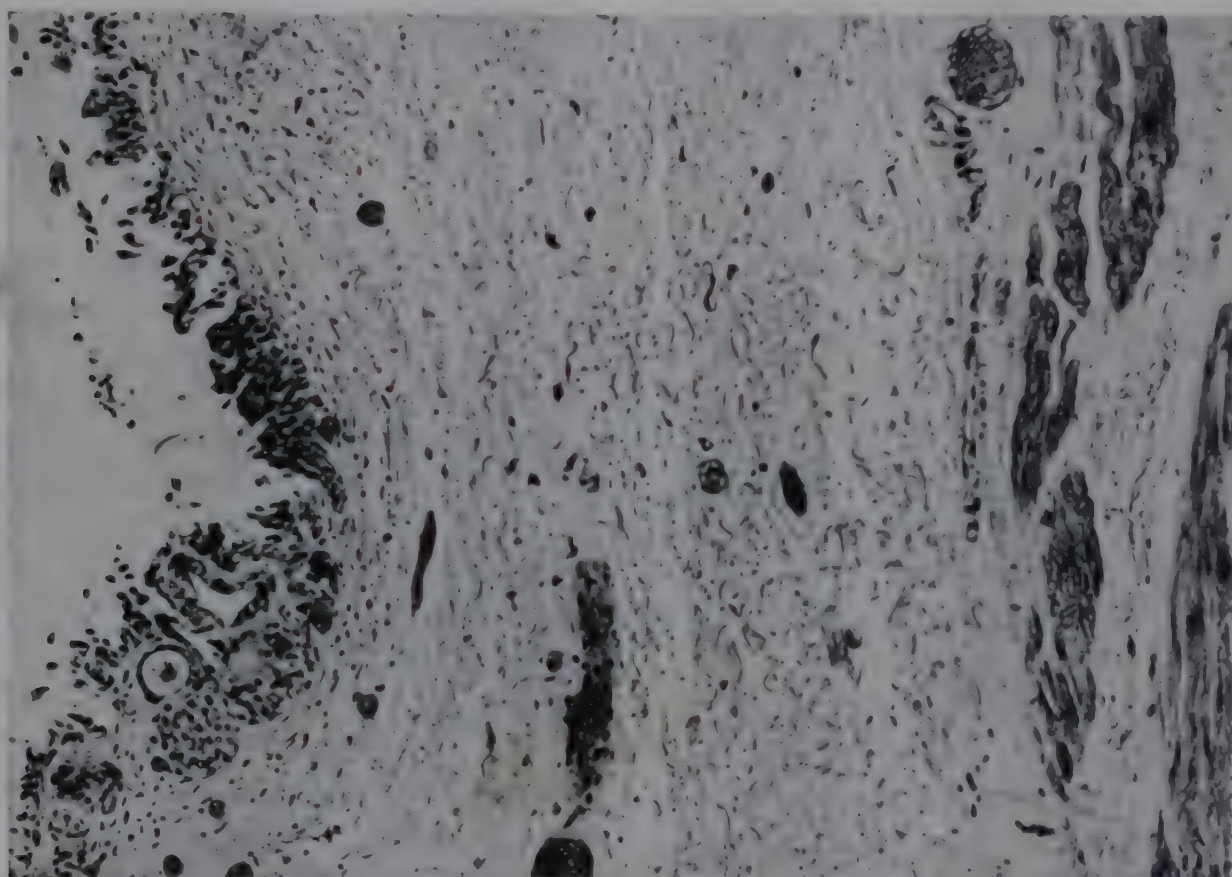


Fig. 379. Acute cystitis, showing the edema of the subepithelial tissue which is the basis of the usual gross appearance of a swollen redundant mucosa in this condition. Note the small epithelial cyst.

free portion, in contrast with a similar ulcer in the trigone, designated "Fenwick's solitary ulcer." When the bladder is distended, two types of pathologic change, intimately admixed, are observed: (1) red, slightly elevated, bleeding granulations; and (2) radiating, irregular, grayish white scars in the wall. Fibrosis and slight to moderate lymphocytic infiltration throughout the entire wall, with destruction of a part of the muscle, are seen. The change is most advanced in the submucosa, and here there are increased vascularity, edema, and conspicuous cellular infiltration with lymphocytes.

Hunner's ulcer is predominantly a disease of women in middle life. The fibrosis of the entire wall and the ulceration of the mucosa

pathways, as in cerebral hemorrhage and transection of the cord. The so-called "automatic bladder" may be established within a month if there are no serious complications.

Cord Bladder. This may follow the paralytic bladder or result directly from a lesion of the central nervous system such as tabes dorsalis. The anatomic characteristics are dilatation and fine trabeculation (not hypertrophic) of the bladder and dilatation of the vesical neck. Clinically, there is diminution or loss of sensation (Emmett and Beare).

Atonic Bladder. Atony of the bladder from a peripheral lesion is difficult to recognize because of the complex interrelation of the three sets of nerves. The organ is dilated and flabby (Braasch; Rose).

Enuresis. Enuresis or bed-wetting is seen largely in children, and may be functional or organic. The organic causes include local lesions such as congenital stenosis of the urethra, phimosis, and irritative lesions of the anogenital region (pin worms, anal fissure, vaginitis, cystitis); and systemic conditions such as diabetes insipidus.

Incontinence. Dribbling of urine means one of two things: disturbance of innervation of the bladder or an abnormality of the musculature of micturition. In both mechanisms there are congenital and acquired types. The most important is injury to the internal sphincter during childbirth.

Frequency. Frequency of urination is the symptomatic expression of an increase in the amount of urine excreted by the kidneys (diabetes), a diminution of the capacity of the bladder (fibrosis of the wall), an increased irritability of the bladder (inflammations), or incomplete emptying at each voiding as the result of vesical or infravesical obstruction (enlarged prostate).

Miscellaneous Lesions of the Bladder

Congenital Anomalies. Complete agenesis, partial or complete duplication, and congenital diverticula have been reported. The bladder may fail to separate from the rectum and a cloaca may persist.

Exstrophy of the bladder is that anomaly in which the anterior wall of the bladder and the corresponding part of the anterior abdominal wall are absent. The posterior vesical mucosa thus forms a part of the abdominal wall. The symphysis is lacking. The exposed mucosa soon becomes irritated and infected, and most patients die before the end of the first decade.

In early fetal life the lumen of the bladder connects with the allantois through the urachus. Persistence of the entire urachus produces an umbilical urachal fistula, which may or may not communicate with the bladder. Isolated segments are urachal cysts lined by columnar epithelium and filled with clear fluid. Rare carcinomas apparently arise in urachal remnants.

Injuries. Rupture of the full bladder by nonpenetrating trauma is almost always in the superior posterior part into the free peritoneal cavity. The extravasated urine incites peritonitis.

Foreign Bodies. All sorts of narrow objects (nails, hairpins, needles) are introduced into the urethra and bladder for one reason or another. In the bladder the foreign body becomes incrustated with salts. Surgical items, such as sutures, catheters, and sponges, have also been observed.

Epithelial Tumors of the Bladder

Our modern knowledge of tumors of the bladder was greatly benefited by the estab-

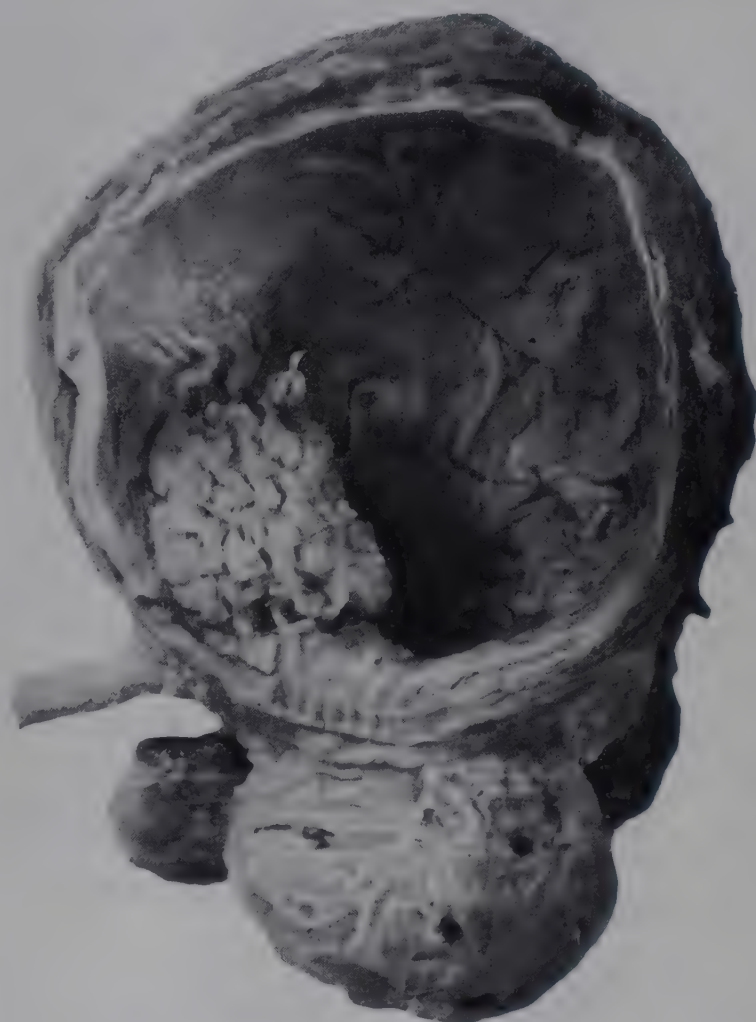


Fig. 380. Papillary epithelial tumor of bladder.

lishment of a registry at the Armed Forces Institute of Pathology (Ash).

Pathologic Anatomy. There are two gross anatomic types of epithelial tumors of the bladder: a sessile, primarily infiltrating type and a papillary type. The latter is the commoner and is observed in 80 to 90 per cent.

Papillary tumors may be coarse, villous masses attached by a narrow pedicle, or broad flat growths. In the relatively benign type there is no invasion at the base, while in the malignant, small yellow or gray foci may be seen in the musculature, and the base is indurated. Two-thirds are located on the posterior wall, in the trigone, or about the vesical neck. In one-third of all patients there are two or more

tumors. The structure varies from that of a simple papilloma covered by typical epithelium to that of a highly invasive neoplasm of anaplastic cells. The Registry has recognized four grades and defines them as follows:

“Grade I are those which others might call ‘simple papilloma’ in which the cell is uniformly of the transitional type, mitoses infrequent and in which there is no histologic or clinical evidence of invasion. Grade II are those in which there is not the uniformity in

demonstrable causal factors. However, there are two known conditions in which vesical neoplasm is frequent—schistosomiasis and exposure to occupational hazards in the aniline dye industry.

Schistosomal Carcinoma. In Egypt where infestation with *Schistosoma haematobium* is high (70 per cent of the male agricultural population over five years of age), associated carcinoma and sarcoma of the bladder in men is present in about 5 per cent. Although

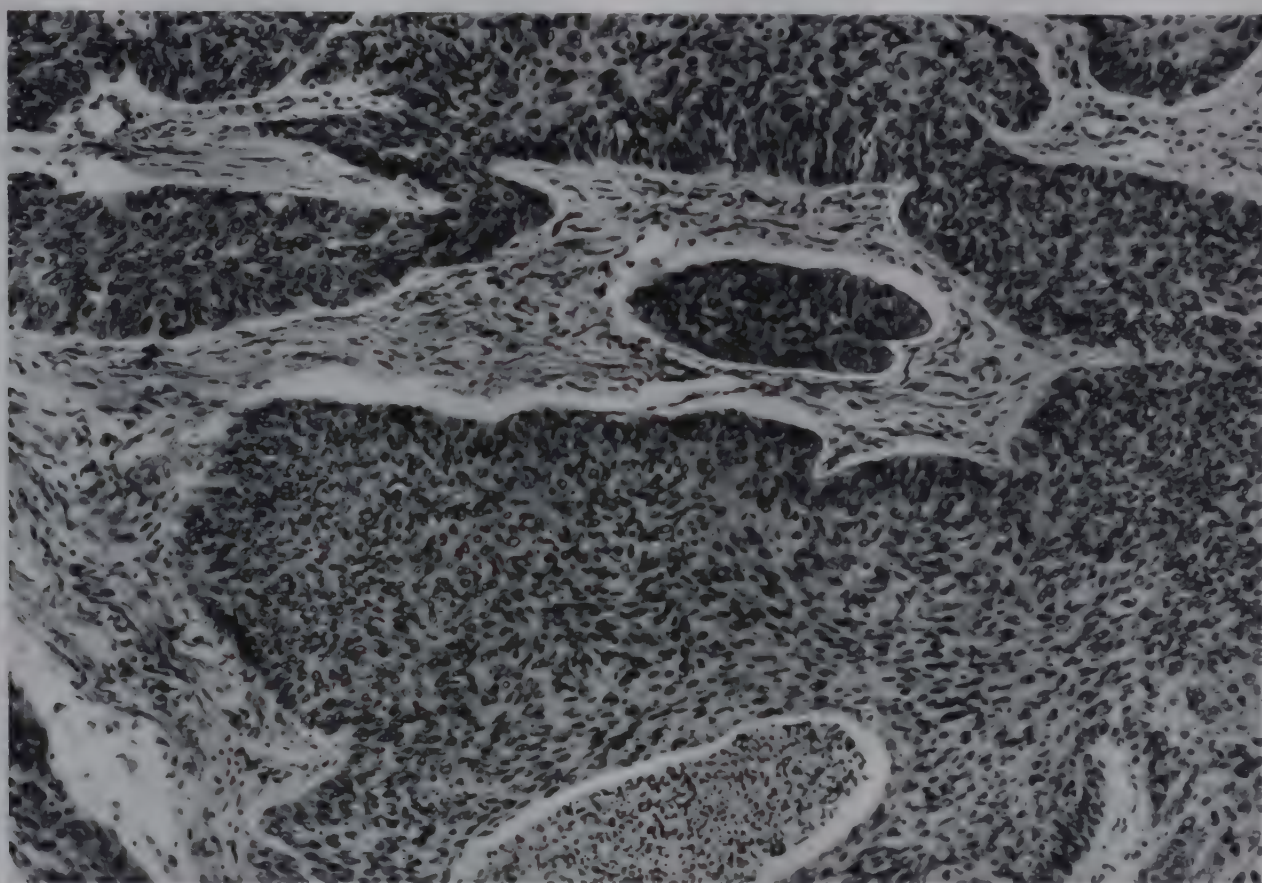


Fig. 381. Papillary carcinoma of bladder.

cell type nor in arrangement, there are more frequent mitoses and there may or may not be histologic evidence of invasion. Grades III and IV are reserved for those showing greater anaplasia, metaplasia either to the squamous or adenomatous type and showing frank invasion.”

Invasive tumors appear as a regional thickening and induration of the vesical wall by white friable tissue. The mucosa is elevated, firm, granular, and friable.

At the time of death, metastases are present in the regional nodes (hypogastric) in 20 per cent and in distant tissues in 15 per cent, chiefly the liver and lungs (Spooner).

Incidence. Over 80 per cent of epithelial tumors are in persons over fifty, with a sex preponderance of 3:1 in men.

Causal Factors. In most patients with an epithelial tumor of the bladder there are no

women also suffer from the infestation, a concomitant tumor is exceptional (Ferguson).

Industrial Carcinoma. A significant percentage of workers in industries in which there is exposure to β -naphthylamine develop papillary tumors of the bladder. The latent period from first exposure to the appearance of the tumor may be as long as forty years. Similar neoplasms have been produced in dogs (Hueper).

Adenocarcinoma of Bladder. This is a rare type of vesical tumor and may be derived from the subtrigonal glands, from remnants of the urachus, or from glands formed in glandular cystitis.

Clinicopathologic Correlation. Correlation is best illustrated by citation of the “average case” registered at the Armed Forces Institute of Pathology (Ash):

“A white male, age 60 years. Chief com-

plaints: Hematuria and dysuria. Cystoscopic examination: Single papillary tumor located on posterior surface of base of bladder. Pathology: Carcinoma, papillary, Grade I or II. Prognosis: Repeated "recurrence" in spite of treatment; has about 1 chance in 3 of living 5 years and about 1 chance in 25 of complete recovery."

The hematuria is caused by ulceration of the tumor, and the dysuria is probably related to disturbances in motility of the bladder and blocking of the vesical orifice by tumor or blood clots. Invasion of the region of the ureteral orifices is followed by obstruction and the consequent hydronephrosis and urinary infection.

The prognosis is better in the papillary than in the infiltrative type. The five-year survival rate varies from 2 to 82 per cent, depending on type of tumor, choice of operative treatment, and additional therapy with radiant energy.

Mesenchymal Tumors of the Bladder

Epithelial tumors of the bladder constitute about 90 per cent of all tumors of this structure. Of the remaining 10 per cent, 8 per cent are benign and 2 per cent are malignant. Among the benign tumors, the more important are the fibroma (Higgins), hemangioma (Ballengier, Elder, and McDonald), leiomyoma (Kretschmer), rhabdomyoma, and neurofibroma (Thompson and McDonald). These tumors appear as sessile or pedunculated masses, extending into and partially filling the lumen of the bladder. They have the same gross and microscopic structure as similar tumors in other parts of the body. There is usually an associated cystitis. The commonest symptom is hematuria from ulceration of the surface of the tumor.

Sarcomas of the bladder correspond in cellular type with the benign tumors; that is, there are leiomyosarcomas (Kretschmer and Doerhing) and rhabdomyosarcomas (Uhlmann, Grossman, and Calvin). Other types are extremely rare. Sarcoma of the bladder grows as an infiltrating mass in the wall or as a pedunculated nodule extending into the lumen of the bladder. The histologic appearance is that of sarcoma in general. Sarcomas of the bladder are most frequent before the age of ten years and after the age of forty-five years.

Metastases are unusual, but should be looked for in the regional lymph nodes, lungs, and liver. Ulceration of the surface of the tumor produces hematuria in about one-half of the cases. No causal factors have been demonstrated.

Congenital Anomalies of the Ureter and Kidneys

The ureters grow out of the side of the lower end of the wolffian duct and project into the mesenchyme, which is designated as the "metanephrogenic ridge."

The ureter may fail to bud on one or both sides, and no structure resembling kidney is then formed—agenesia. The ureter may develop but the metanephrogenic tissue fail to differentiate into a functional kidney—aplasia. Failure of full maturation leaves a small but functional kidney—hypoplasia.

Two buds may grow out and persist as a complete double ureter or the single bud may bifurcate at any point from the bladder to the renal hilum—partial double ureter or bifid pelvis. With two vesical orifices the ureter from the upper pelvis is located caudally.

In the absorption of the wolffian duct into the cloaca and separation of the bladder and genital tract, the ureteral orifice may be carried over into the urethra, seminal tract, or vagina.

Two ureteral buds on one side may be capped by distinct kidneys—supernumerary kidney. If one ureteral bud crosses to the opposite side, there are two kidneys on one side—crossed ectopy. Fusion of the two kidneys at the caudal poles is one of the most frequent anomalies—horseshoe kidney (Fig. 382). Failure of ascent of the kidney results in the pelvic kidney: a flattened organ with the hilum on the anterior surface in the arch of the bifurcation of the aorta (McCrea).

Duplication or triplication and anomalous branching of the vessels are common and important because an occasional anomalous vessel to the lower pole of the kidney causes obstruction at the ureteropelvic junction.

Nephroptosis

The normal kidney is embedded in the retroperitoneal fat and moves with respiration. If the lower pole can be palpated on standing or on deep inspiration, it is abnormally mobile.

Pathologic Anatomy. The kidney may be of normal shape, or deformed because of pressure against other structures. The structures in the pedicle are usually elongated.

Incidence. Causal Factors. Some degree of nephroptosis is demonstrable in about 20 per cent of women and 1 per cent of men (Kidd). The right kidney is more frequently involved than the left in women. Causal factors are not definite, but abnormal body build, relaxa-

result from compression of the renal artery (McCann).

Orthostatic Albuminuria. This syndrome, characterized by albuminuria only while maintaining an erect position, is apparently caused by pressure on the left renal vein by the protrusion anteriorly of a lordotic spine in the upright position.

Essential Hematuria. Rarely, hematuria cannot be explained by the clinical and radio-

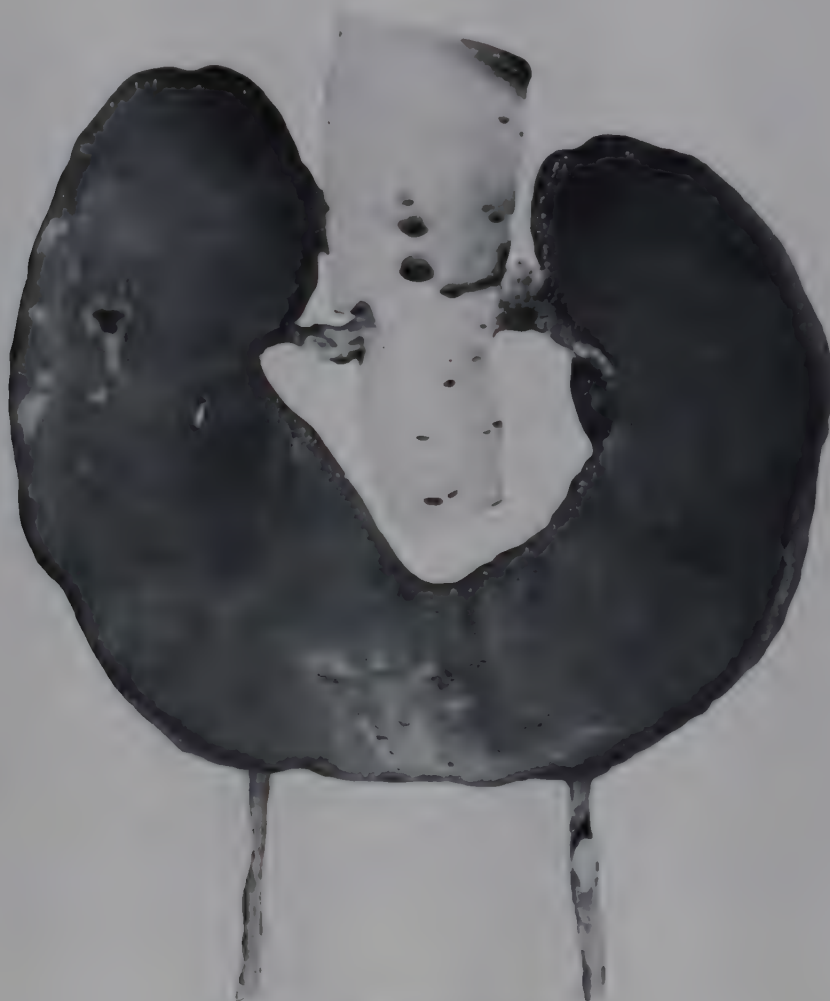


Fig. 382. Horseshoe kidney.

tion of the abdominal muscles, trauma, and inadequate fat pads have been postulated.

Clinicopathologic Correlation. Only about one-fourth of women with nephroptosis complain of symptoms referable to it. The symptoms are related to the effects of interference with structures in the pedicle: pain from congestion of the kidney secondary to compression of the vessels; indefinite abdominal discomfort from stretching of the nerves; and Dietl's crises from angulation of the ureter and acute hydronephrosis.

Orthostatic Hypertension. A few persons with nephroptosis have vascular hypertension only in the standing position. In at least some there is a demonstrable decrease in total renal blood flow in the erect position, assumed to

graphic examination. Occasionally the loss of blood is extreme, and nephrectomy must be carried out. Anatomic examination may reveal a small cavernous hemangioma in a papilla, or may be entirely negative (Webb-Johnson and Warwick).

Papillary Tumors of the Renal Pelves and Ureters

As in epithelial tumors of the bladder, papillary tumors of the embryologically identical lining of the ureters and pelvis are frequently multiple, and the distinction between the benign and malignant types by histologic examination is not definite.

Pathologic Anatomy. The individual tumors are soft or firm, sessile or pedunculated

masses extending into the lumen. The papillary structure is frequently conspicuous, and a large branching neoplasm may originate from a relatively small base.

In the benign type the papillae are covered by an orderly layer of transitional epithelium, and supported on a delicate, richly vascularized stalk. All grades of anaplasia from this to highly atypical spindle cells are seen. Small or large foci may show a squamous type of cell with keratinization.

A rare pelvic tumor is of the solid and invasive type.

appear within three years (Kimball and Ferris).

Incidence. Papillomatous tumor of the pelvis and ureter is a disease of men (3:1), with the highest incidence between thirty and seventy years. Bilateral lesions are present in about 5 per cent. The renal pelvis is the commonest site, and about one-fourth of all examples are multiple (Thomas and Regnier).

Clinicopathologic Correlation. As would be expected with a vascularized neoplasm growing into the urinary tract, the usual initial sign is hematuria from ulceration and hemorrhage.

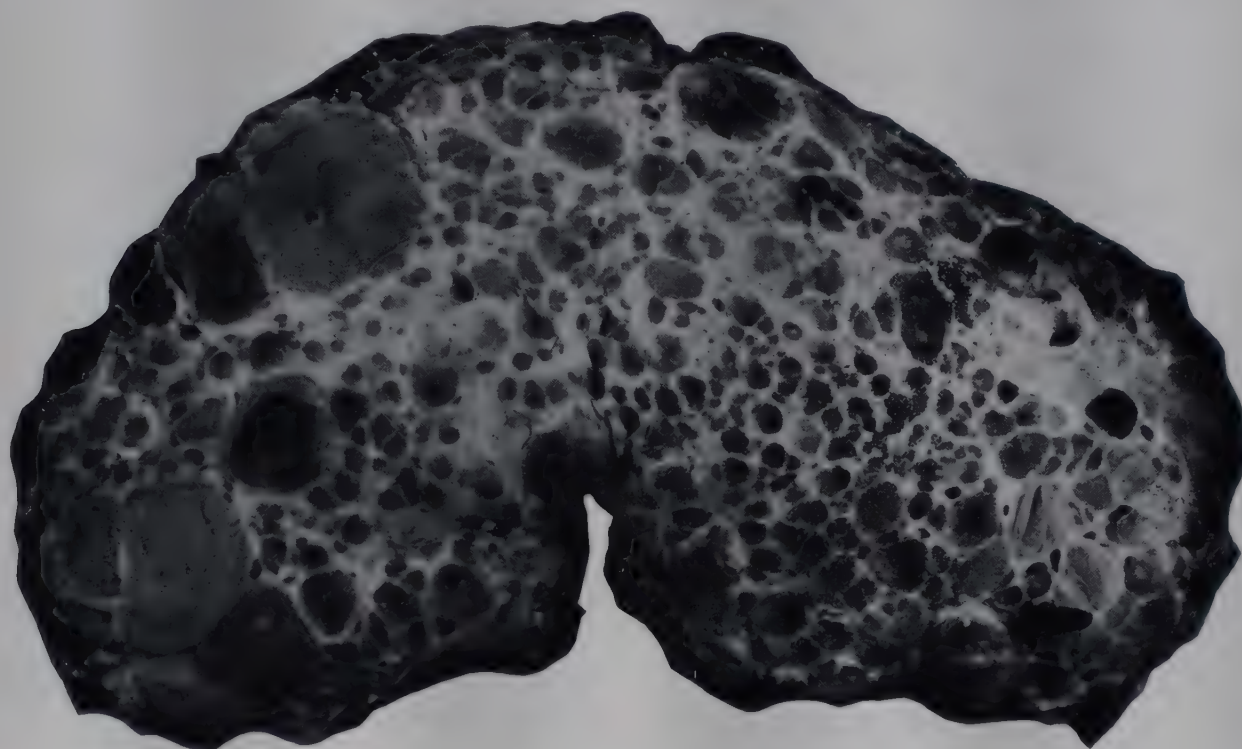


Fig. 383. Polycystic kidney.

Histogenesis. There is no question concerning the origin of these tumors from the epithelium lining the pelvis and ureter, but one school holds that the tumors are of multiple independent origin, while the other school believes that some at least are implantation metastases (Kimball and Ferris).

Grading. Prognosis. The usual histologic criteria are inadequate to differentiate the benign and malignant types. Recurrence in some part of the urinary tract is observed in two-thirds of patients after removal of the primary tumor, whether diagnosed benign or malignant. Hence it seems desirable to consider all papillary tumors of the urinary tract potentially malignant, and to treat them by radical removal of the kidney and ureter, including the intramural part. Five-year survivals with this technique should be about 75 per cent. Most recurrences are in the ureteral orifice or the vesical mucosa about it, and 85 per cent

The fact that the lesion is space-consuming is responsible for the radiographically diagnostic deformity of the pelvis. Occlusion of the ureter by a blood clot or by the tumor causes the pain.

Polycystic Disease of the Kidneys

There are three types of cysts of the kidney, polycystic disease, solitary cysts, and retention cysts. From a clinical standpoint, polycystic disease is the most important (Bell).

Pathologic Anatomy. The kidneys are greatly enlarged. In adults they weigh from 1000 to 2000 gm. and in newborn children from 100 to 1000 gm. The surface is composed almost entirely of projecting cysts, varying in size from a few millimeters to several centimeters. The cysts are filled with clear, limpid fluid, with cloudy fluid, or with light-brown, coagulated masses. Occasionally, there is hemor-

rhage into the cysts, or suppuration of the cystic content. On the cut section the cysts are seen to make up the greater part of the bulk of the kidneys. Between them there are narrow trabeculae in which small remnants of renal parenchyma may be grossly demonstrable. There is no distinction between cortex and medulla. A few of the cysts may communicate with the pelvis, and this is a possible explanation for the appearance of blood in the urine.

The cysts are lined by a flat or cuboidal cell, supported on a fibrous tissue capsule. Projecting into the cyst a glomerulus may occasionally be seen, and rarely a short segment of an open tubule leaves the cyst wall at one point.

The pelvis is greatly elongated, and the calices project laterally at right angles. The ends of the calices are rounded. All of these changes in the pelvis are readily seen in pyelograms, and the picture is pathognomonic for polycystic disease.

In over 90 per cent, both kidneys are involved, but undoubted unilateral polycystic disease occurs in from 5 to 10 per cent.

Pathogenesis. It is apparent that the cause of the polycystic kidney must be sought in the development of the kidney. The most acceptable explanation is a failure of the involution of the first few generations of glomeruli and tubules. Normally, these lose their connection with the collecting tubules and atrophy (McKenna and Kampmeier). The cysts so formed enlarge, but apparently no new cysts develop in later life.

Incidence. There are two peaks of age incidence, one at birth and the other in the fifth decade, with rare examples in the first decade and a few in the other decades. There is no difference in the two sexes. A familial incidence has been observed. Congenital anomalies of other organs are a not unusual association. Polycystic disease of the liver, pancreas, and lungs is rare, but when it is present the kidneys are almost always involved.

Clinicopathologic Correlation. Signs and symptoms are related to the presence of masses in the region of the kidneys and renal insufficiency. The latter usually comes on gradually as the result of compression atrophy of the functional renal parenchyma by progressive growth of the cysts.

Elevation of blood pressure and slight hy-

pertrophy of the heart occur in about half of the cases in adults. If there is hypertension, the secondary changes of arteriolosclerosis in all organs are present, and death may be caused by cerebral hemorrhage.

Although some patients may live for many years, half die within four years after the diagnosis is made.

It should be remembered that a polycystic kidney may be the seat of any disease which affects the kidney: calculi, tumors, tuberculosis, and pyogenic infections.

Solitary Cyst of the Kidney. Solitary cysts of the kidney, usually in the cortex and projecting from the surface, may be small or large. In the latter type there are obscure symptoms of a mass in the region of the kidney. The cyst is lined by cuboidal or flat cells, and the fluid is characteristically colorless and limpid. The cause and pathogenesis are unknown, but it is probable that they are congenital.

Retention Cysts. In all types of chronic renal disease—arteriolar nephrosclerosis, chronic glomerulonephritis, and chronic pyelonephritis but predominantly in nephrosclerosis—small cysts are present in the cortex. The cysts are lined by cuboidal cells and filled with a colorless limpid fluid. The cause presumably is obliteration of a segment of a tubule by fibrous tissue.

Focal Hyperplasia and Adenoma of the Kidneys

Pathologic Anatomy. In kidneys with nephrosclerosis, small subcortical cysts, yellow circumscribed nodules, and all variations between the two are frequently seen.

The cysts are rarely over 5 mm. in diameter. The contained fluid is clear and limpid, and the lining is a single layer of darkly staining cuboidal cells. At one or more points there are simple or branching papillae extending into the lumen.

The nodules which grossly appear solid are essentially the same except that the cyst is filled by branching intertwined papillae. There is no distinct capsule, and frequently a typical darkly staining epithelial tubule is seen among the immediately adjacent renal tubules. Occasionally, the structure is distinctly acinic. The size varies from less than a millimeter to several centimeters.

A variety of diagnostic terms may be used: cyst, papilliferous cyst, papillary cystadenoma, or tubular adenoma. Further, there is a gradual transition from one to the other. The association with nephrosclerosis and the lack of

seems probable that some carcinomas arise in benign tumors and focal hyperplasia of an arteriosclerotic kidney (Trinkle).

Benign Tumors of Mesenchymal Tissue. The so-called "fibroma" of the renal pyramid

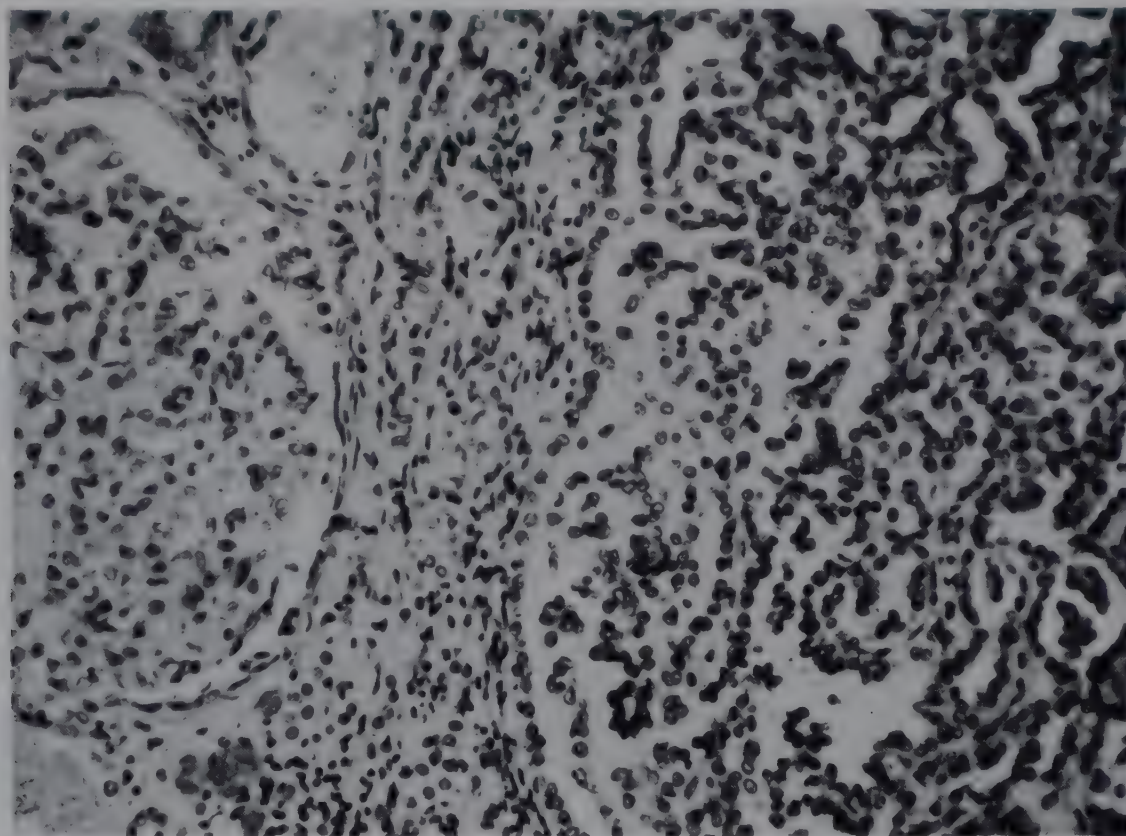


Fig. 384. Focal hyperplasia of renal tubules.

association with other types of chronic renal disease indicate a causal relation to ischemia.

Relation to Carcinoma. Some of the larger solid nodules contain foci with cells and a

—probably a hamartoma—has been described elsewhere (p. 146). Rarely, true fibromas, lipomas, and myxomas of the kidney, renal hilum, and renal capsule are seen.



Fig. 385. Renal cell carcinoma. (Photograph by courtesy of Dr. Lauren Ackerman.)

structure identical with that of carcinoma of the kidney. Rarely, a small tumor of this sort will show invasion of veins, as in a carcinoma. Although the evidence is largely inferential, it

Carcinoma of the Kidney

Since 1883 a controversy has raged concerning the origin of a characteristic tumor of

the kidney known as "Grawitz's tumor," "hypernephroma," "hypernephroid tumor," and "renal cell carcinoma."

Pathologic Anatomy. Gross Appearance. Carcinoma of the kidney is typically a solitary, circumscribed, spherical tumor composed of yellow, friable tissue divided into lobules by thin trabeculae. There is, over most of the tumor, a definite fibrous capsule, and the renal parenchyma is compressed. At some points, particularly in relation to the pelvis and great veins, the capsule is lacking and neoplastic tis-

with a clear or granular cytoplasm (Stirling and Ash).

In my own experience the distinction between the two types is largely artificial, since multiple sections of any one tumor frequently show both varieties of cellular structure and architectural arrangement.

Extension and Metastases. The carcinoma of the kidney characteristically invades the renal pelvis and the renal vein. In the former it is seen as a fungating, ulcerated projection, while in the latter it appears as a solid cord

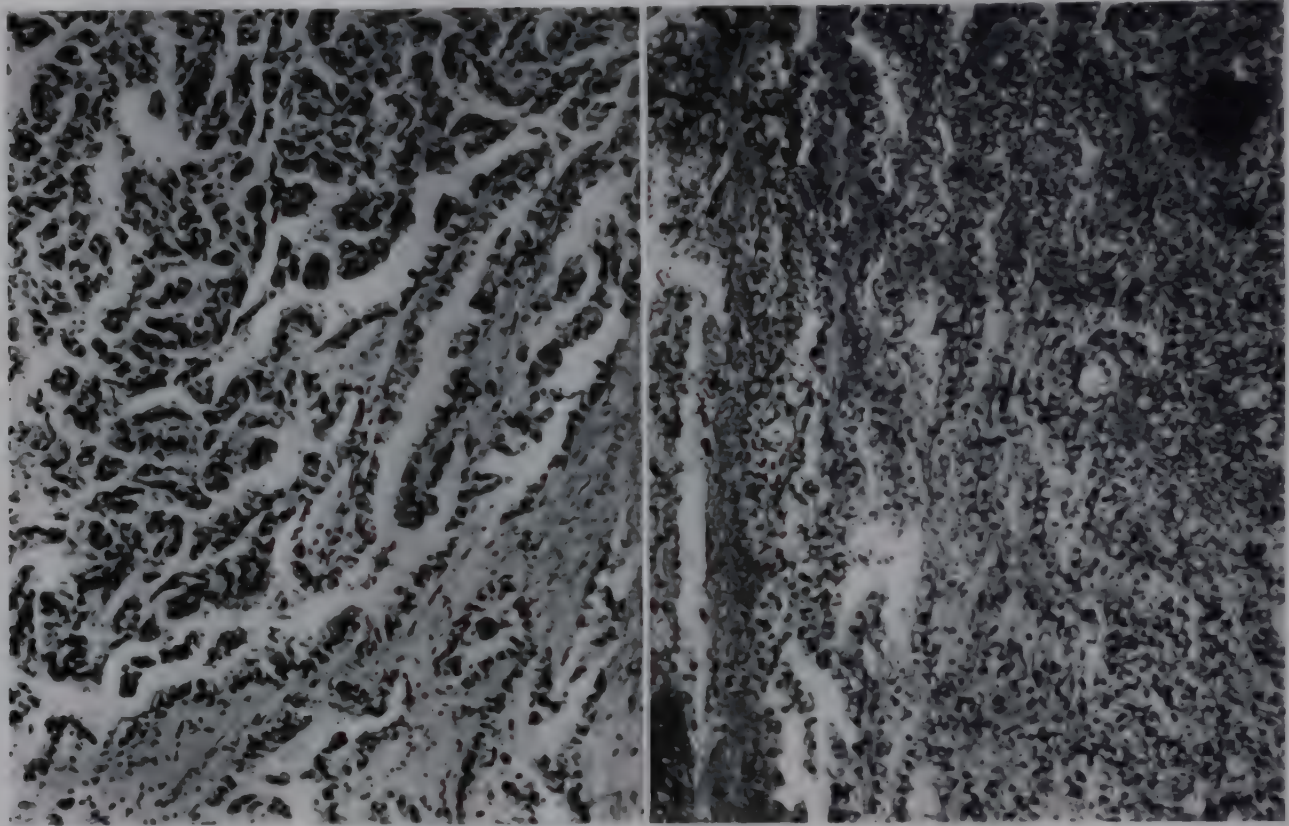


Fig. 386. Two types of histologic and cytologic structure in a renal cell carcinoma.

sue projects directly into the pelvis and venous channels. Throughout the tumor, degenerative changes are prominent: hemorrhage, necrosis, and cyst formation. Less commonly, calcification is observed. In large tumors the greater part may undergo necrosis, leaving only the capsule and a thin rim of surviving cells.

Microscopic Appearance. There are two general types of architecture and cytologic structure; one resembling the adrenal cortex and the other the renal epithelium (Fig. 386).

The hypernephroid type shows numerous small islands of clear cells without lumens, separated by delicate, vascularized, connective tissue septa. The cells are large. The cytoplasm is clear or foamy, and the nuclei are small and hyperchromatic.

The nephroid type is characterized by formation of acini or larger cystic spaces with papillae, lined by cuboidal or columnar cells

composed partly of neoplastic tissue and partly of thrombus, filling the vein.

Metastases to the periaortic nodes about the renal artery and aorta are of relatively little significance as compared to the vascular metastases. The "tumor thrombus" in the renal vein may extend into the vena cava as far as the right atrium. Secondary nodules are most frequently seen in the lungs, liver, bones, and brain.

Histogenesis. There are two ideas concerning the origin of carcinoma of the kidney: from adrenal rests and from renal epithelium. Those who favor an origin in the kidney point to the rarity of similar tumors in the adrenal, and the uniform distribution in the kidney while adrenal rests are found largely about the upper pole. On the other hand, some investigators have divided the tumors into two groups and find a difference in prognosis: good in

hypernephroma; and poor in hypernephroid or renal carcinoma (Rose). There are no absolute criteria for solution of the problem (Schiller).

Incidence. The highest incidence is between thirty and seventy years. The sex preponder-

ulcerated tumor growing into the renal pelvis: palpable mass, hematuria, and filling defect of pelvis on a pyelogram.

Extrarenal Hypernephroma. Tumors with a gross and microscopic structure similar to that of the renal cell carcinoma are rarely seen

TABLE 46. DETERMINANTS OF PROGNOSIS IN CARCINOMA OF KIDNEY

Weight of Involved Kidney (Gm.)	Per Cent Five-Year Survivals of Those Discharged from Hospital after Nephrectomy	
	With Invasion of Vein	Without Invasion of Vein
0 to 400.....	33.3	53.8
500 to 999.....	26.3	54.5
Over 1000.....	18.7	46.4

ance is 7:3 in favor of men. Rarely, bilateral tumors occur (Beilin and Neuman). Little is known concerning causative factors. Some carcinomas of the kidney appear to be derived from benign tumors (see p. 789).

outside the kidney: in the retroperitoneal tissue, ovary, broad ligament, and testis (Barney). If they are derived from rests of adrenal cortex, most are from the androgenic cells, and hence not comparable to the renal neo-

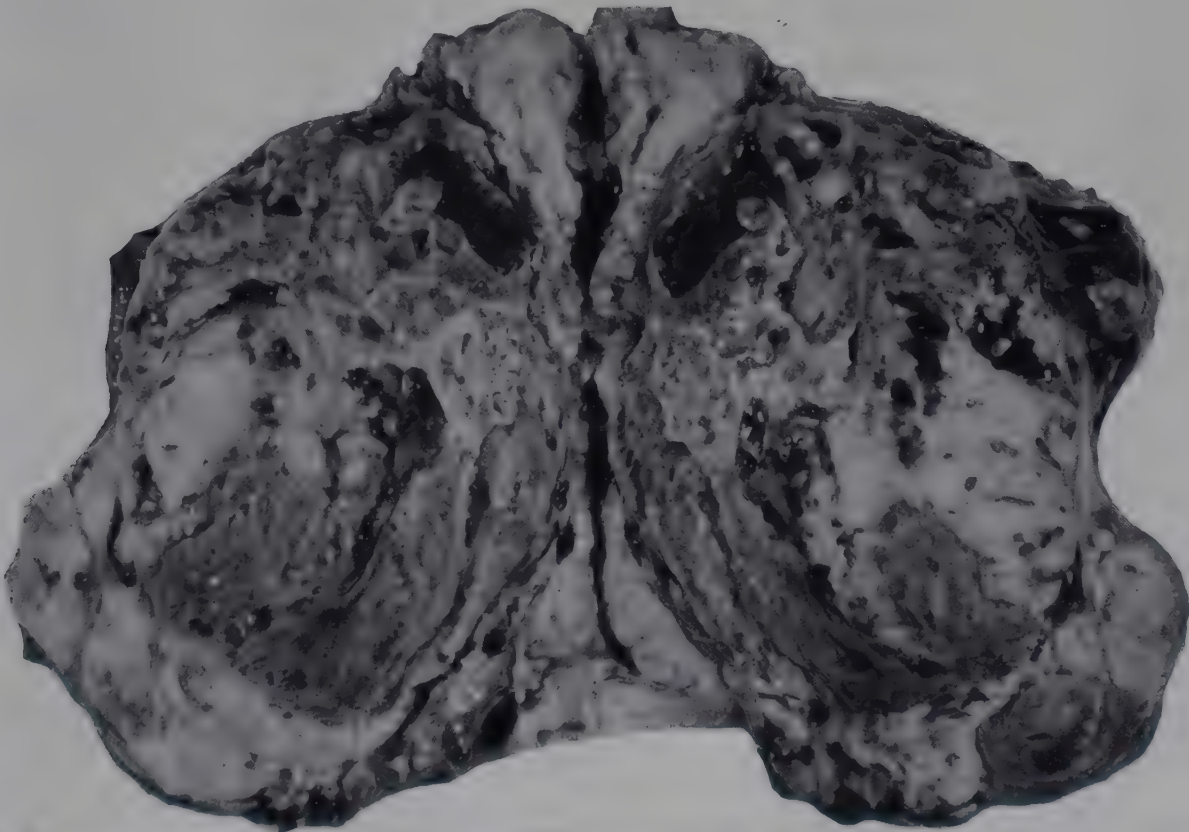


Fig. 387. Embryonal nephroma of kidney. (Photograph by courtesy of Dr. Lauren Ackerman.)

Clinicopathologic Correlation. Growth of the tumor is relatively slow. The grade influences the prognosis. The average five-year survival rate does not exceed 25 per cent (Hand and Broders). Other important factors in determining prognosis are invasion of the renal vein and size of the tumor, as shown in the statistics of McDonald and Priestley (Table 46).

The signs and symptoms are those of an

plasm. See further discussion on tumors of the ovary (p. 884), interstitial cell (p. 894), and the adrenogenital syndrome (p. 851).

Embryonal Nephroma of the Kidney

A distinctive tumor of the kidney, designated variously as "Wilms' tumor," "adenomyosarcoma," or "embryoma," occurs usually

in children, rarely in adults (Weisel, Dockerty, and Priestly).

Pathologic Anatomy. The tumors are, at the time of observation, large, lobulated, fleshy, and gray. There is a dense fibrous capsule, and the remaining renal parenchyma is stretched over the surface in one or more regions. The cut section shows division into large lobules by connective tissue trabeculae. Foci of hemorrhage, necrosis, and cyst formation are common.

There are two dominant cellular types: small, spindle-shaped, undifferentiated, mesenchymal cells; and cuboidal, darkly staining, epithelial cells, oriented into irregular acini with or without a papillary structure. In addition, striated muscle cells, smooth muscle cells, cartilage, and bone are seen. In a given tumor, any one of the types is conspicuous, or there is a general mixture of all. Metastases occur chiefly in the lung and liver.

Histogenesis. The duplication of all cells derived from the somite corresponding to the metanephrogenic ridge suggests that the nephroma is derived from undifferentiated tissue of a somite. Causal factors are unknown.

Incidence. Most nephromas are observed in children before the fifth year, without predilection for either sex or for the left or right kidney.

Clinicopathologic Correlation. Children rarely note early signs and symptoms, and as the neoplasm grows rapidly the first sign in half of patients is enlargement of the abdomen or a palpable mass. Prognosis is poor. About 20 per cent live three years after nephrectomy (Mixer, Ladd and White).

Tumors in Animals. The nephroma is one of the commonest tumors of swine, and in many instances the differentiation into glomeruli is conspicuous (Feldman). It is also seen in rabbits (Greene).

Sarcoma of the Kidney

As distinguished from perinephric sarcoma and sarcoma of the retroperitoneal tissue, malignant mesenchymal tumors derived from the structural framework of the kidney form large bulky masses. Spindle cell sarcoma, presumably fibrosarcoma, is the commonest type. Liposarcoma has been reported (Froug). The prognosis is poor, and even with surgical re-

moval and irradiation most patients are dead within a year (Judd and Donald).

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XCI

Causes and Effects of Obstruction of Veins

The function of a vein is to provide an unobstructed closed channel for the return of blood to the heart. Factors that drive or pull the blood toward the right atrium are: contraction of the ventricles, negative pressure within the thorax, action of the right side of the heart, squeezing of the veins during muscular activity, and gravity. Physiologically, the most important alteration is an increase of venous pressure because of a failure of one or more of these factors or because of actual obstruction to a vein.

Phlebectasia

Dilatation of veins, or phlebectasia, is of major clinical importance in three regions of the body: the lower extremities (varicose veins), the pampiniform plexus (varicocele), and the internal and external hemorrhoidal system (hemorrhoids or piles).

Varicose Veins. Varices of the lower extremities affect the superficial system, usually the long saphenous vein. Early, the veins are dilated, especially just below the valves, and the media is hypertrophic. With increasing size the valves become incompetent, and there is atrophy of the muscular and elastic fibers of the wall as well as fibrosis (phlebosclerosis). In late stages there may be calcification of the walls, thrombi within the lumen in all stages of organization, and fibrosis of the adventitial tissues with adherence to the surrounding structures. The skin in the region affected by the varices is thickened, indurated, and pigmented. One of the most troublesome complications is chronic ulceration following traumatism (varicose ulcers). Because of the anoxia of the tissues, the ulcers heal slowly and become infected.

Varicose veins are commoner in men than in women. The most important causal factor

appears to be an increase in venous pressure and possibly a congenital absence of valves.

Varicocele. The veins of the pampiniform plexus if dilated form an elongated mass of anastomosing channels, easily palpable through the skin. The walls are atrophic and fibrotic. The condition is more common on the left than on the right, probably because of the greater length of the left spermatic vein, the higher pressure in the left renal vein than in the vena cava (the right spermatic vein enters the vena cava), and pressure on the left vein by distention of the sigmoid colon.

Hemorrhoids. Dilatation of the hemorrhoidal veins may involve either the superior veins (internal hemorrhoids) or the inferior veins (external hemorrhoids). The former are arranged in three groups: right anterior, right posterior, and left lateral. The latter are superficial to the external sphincter, and bulge as longitudinal folds, radiating from the anus. The pathologic changes are dilatation, adventitial fibrosis, and thrombosis. Infection and ulceration with hemorrhage are common. The direct cause is increase of venous pressure from straining at stool, direct pressure from an enlarged prostate or gravid uterus, and defective venous return in cardiac failure and cirrhosis of the liver.

Obstructive Venous Disturbances

Obstruction of a vein may be intrinsic, by a thrombus within the lumen, or extrinsic, by pressure from without. The thrombus may form because of alterations in the flow of blood (bland thrombus), or because of infection of the wall (thrombophlebitis). Aside from the importance of the secondary changes in the area drained by an obstructed vein, thrombi in the systemic or portal venous systems may be carried as emboli to the lungs or

liver, respectively. If these emboli are bland, infarcts result; if infected, multiple abscesses of these organs form (see sections on pulmonary embolism, p. 765, and pyelephlebitis, p. 297).

Phlegmasia Alba Dolens. In a few patients following pregnancy, or occasionally following an operation on the pelvis, there is, during the first week, a marked swelling of the leg associated with thrombi in the deep or superficial veins or both. In from seven to fourteen days this swelling subsides, and after one or two months there is again a slight swelling, which persists for months or years. Since these time intervals correspond to the period of lactation, the condition is popularly known as "milk leg." The leg is slightly to moderately swollen, and is pale. There is slight indefinite pain in various parts of the leg or thigh. This condition appears to be a combination of thrombosis in the veins and occlusion of the lymphatic channels. It differs from ordinary thrombosis in that there is marked induration in the adventitial tissue of the veins, and it is therefore a true thrombophlebitis (Homans).

Obstruction of the Superior Vena Cava. The causes of obstruction of the superior vena cava are in order of frequency: aortic aneurysm, carcinoma of the bronchi, primary thrombosis, and mediastinal tumors (Hinchshaw). The venous pressure in the upper half of the body is elevated with consequent edema, congestion, and cyanosis. There is an extensive collateral circulation over the chest wall to the azygos vein and the inferior cava.

Obstruction of the Inferior Vena Cava. Obstruction of the inferior vena cava may result from four general types of disease: primary thrombosis, invasion of the lumen by tumor, pressure from outside, and congenital anomalies. The most important agent in thrombosis is the general disease condition known as "migratory thrombophlebitis." Invasion and obstruction of the lumen by tumor is a frequent sequela of hypernephroma of the kidney and of teratoma of the testis. Pressure from outside may result from any one of a wide variety of lesions: tumors of the retroperitoneal tissues, metastatic carcinoma of the periaortic lymph nodes, and large abscesses or cysts of retroperitoneal tissues or of the liver. Congenital absence of the inferior vena cava is extremely rare.

Collateral Circulation. There are two gen-

eral groups of anastomoses following obstruction of the inferior vena cava: (1) with the superior vena cava through the epigastric, the azygos, hemiazygos, and lumbar veins; (2) to the portal vein, through the uterine or spermatic veins.

Clinicopathologic Correlation. Signs and symptoms of obstruction of the inferior vena cava result from the obstruction and from the disease producing the obstruction. The position, the extent, the rapidity, and the completeness of the obstruction determine the exact signs and symptoms produced (Pleasant).

Obstruction of the Portal System. The most common cause of obstruction of the portal venous system is cirrhosis of the liver. Thrombotic occlusion is also a common complication of pyelephlebitis following acute appendicitis, chronic ulcerative colitis, and other inflammations of the portal drainage areas (see section on cirrhosis of the liver, p. 607). In association with patency of the umbilical vein, portal hypertension and splenomegaly constitute Cruveilhier-Baumgarten's syndrome (Valk and Horne).

Splenic Anemia. Splenic anemia (Banti's syndrome or congestive splenomegaly) is characterized by enlargement of the spleen, hypochromic anemia, leukopenia, and development of extensive collateral venous circulation in the esophagus.

PATHOLOGIC ANATOMY. The spleen is greatly enlarged. The capsule is thickened and the trabeculae prominent. The substance is firm and dark red. The sinusoids of the red pulp are dilated and lined with cuboidal cells. The pulp cords are conspicuous, relatively acellular, and made up largely of thickened reticulum and collagen. The malpighian bodies are small. About some central arteries there are recent hemorrhages, or so-called "siderotic" nodules of older hemorrhage (McMichael). In about half of the cases there is an associated nodular cirrhosis of the liver, and in about a quarter there is occlusion of the splenic vein by an organizing or organized canalized thrombus. In most there are varices of the esophageal veins. The bone marrow shows normoblastic hyperplasia.

CAUSAL FACTORS. The bulk of evidence today supports the concept that splenic anemia is the result of portal hypertension (Thompson). It occurs with equal frequency in both

sexes, and the onset is usually before the age of thirty years. Splenectomy is distinctly valuable in about half the cases, probably in that half not related to cirrhosis of the liver. The usual cause of death is an exsanguinating hemorrhage from rupture of the esophageal varices.

Miscellaneous Venous Obstructions. Thrombi within the dural sinuses and the internal jugular vein are usually secondary to infection of the brain, of the middle ear and sinuses, of the regions of the nose drained by

ing strenuous muscular exercise, thrombosis of the axillary vein occurs (O'Regan).

Migratory Venous Thrombosis

This condition, usually designated "migratory thrombophlebitis," is characterized by recurrent thrombosis in short segments of many peripheral and visceral veins, but little or no inflammatory reaction. Complicating embolism is rare. During each attack the region involved is swollen, red, and tender, and

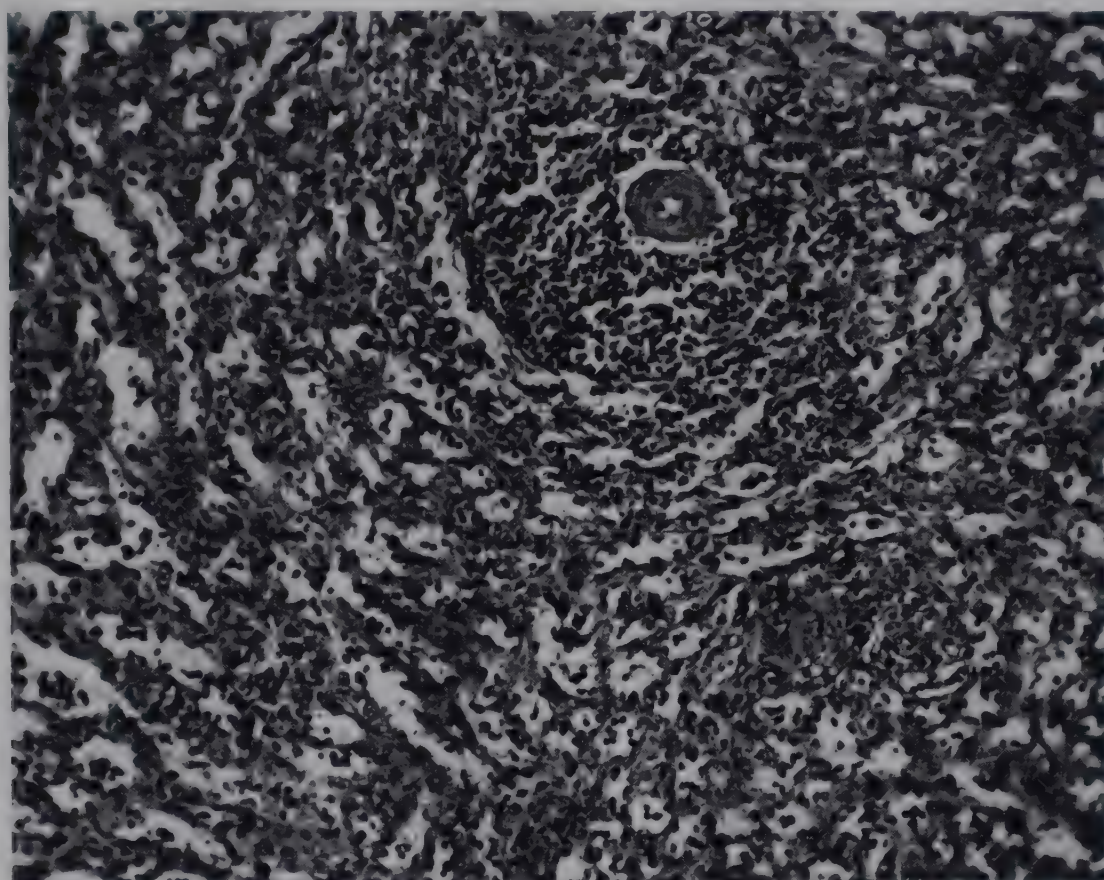


Fig. 388. Spleen in splenic anemia (Banti's disease).

the angular vein, and of the tissues of the orbit. Primary thrombosis of the sinuses is occasionally seen in newborn infants as a part of birth trauma, and in older children with advanced dehydration and emaciation. In some instances, especially in complete occlusion of the superior longitudinal sinus, there is hemorrhagic infarction of the adjacent parts of the cerebral hemispheres. Thrombosis in the renal veins is associated occasionally with infection of the kidney, and commonly with renal carcinoma. Thrombotic occlusion of the mesenteric veins is secondary to infections of the intestine, and almost every case results in infarction of the intestine (Giamarino and Jaffe). Thrombosis of the coronary sinus of the heart apparently has no effect on the structure of the myocardium (Warner and Dauphinee). In an occasional young person follow-

there is a systemic reaction with fever and leukocytosis. The veins of the extremities, the inferior vena cava, and the dural sinuses are the most common sites.

The cause is obscure. Some examples are associated with carcinoma of the body and tail of the pancreas.

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XCII

Causes and Effects of Obstruction of Lymphatics

The lymphatic system is a closed system of capillaries and larger vessels, the function of which is to provide channels for the return of extravascular fluid into the blood.

Chylous Transudates

The lymph is collected into two principal vessels, the thoracic duct and the right lymphatic trunk, which empty into the left and right subclavian or jugular veins, respectively. If the thoracic duct is obstructed or torn, chyle may accumulate in the serous cavities, but in most instances the anastomoses of the lymphatics of the thoracic wall are so rich that a collateral circulation is quickly established.

Chylous Ascites. The common causes of accumulation of chyle in the peritoneal cavity are retroperitoneal and mediastinal tumors with extrinsic pressure on the thoracic duct and direct invasion of the duct by neoplastic cells. Increasing pressure within the vessels may cause rupture into the urinary tract and consequent chyluria. Filling of the scrotal sac with chyle—chylocele—is usually caused by filariasis.

Chylothorax. Chylothorax is most frequently observed following trauma with tearing of the thoracic duct in the posterior mediastinum. Other causes are pressure from a neoplasm or tuberculous nodes, and blockage of the duct by neoplastic tissue growing within it. In a significant number of cases in children no cause can be demonstrated (Everhart and Jacobs).

Chronic Lymphedema

Progressive enlargement of one or more extremities or of the scrotum or vulva, with thickening and induration of the skin, has been known since ancient times, and has been called "elephantiasis." The term "lymphedema" is more definitive.

Pathologic Anatomy. The leg or arm is enlarged to three or four times normal size. The skin is thickened and frequently darker than normal. The dermis is firm and fibrotic. Throughout the subcutaneous fibro-adipose tissue there are interlacing trabeculae of fibrous tissue with quantities of interstitial fluid. Immediately overlying the deep fascia there is a large accumulation of partially clotted white fluid and thickening of the superficial layer of the fascia by fibrous tissue. The veins in all parts of the extremity are normal or dilated. Microscopically, the epidermis shows hyperkeratosis with atrophy of the underlying layers. The dermis is fibrotic, but immediately beneath the epidermis there are slight edema and infiltration with lymphocytes. The epidermal alterations are similar to, if not identical with, ichthyosis. In the deeper tissues there are edema and slight infiltration with lymphocytes and mononuclear cells. In genital lymphedema the gross and microscopic alterations are the same (De Savitsch).

Types and Causal Factors. Chronic lymphedema is undoubtedly the direct result of obstruction of the flow of fluid in the lymphatics, either anatomic or physiologic. Any pathologic process which brings about this obstruction may be a causal factor. *Wuchereria bancrofti* (*Filaris bancrofti*), which gains entrance to the lymphatics and occludes them, has long been known as a causal agent, but noninflammatory types of the disease have been observed. The following classification would appear to be the most satisfactory at present (Allen and Ghormley):

- I. Noninflammatory
 - A. Primary
 1. Praecox
 2. Congenital
 - (a) Simple
 - (b) Familial (Milroy's disease)

B. Secondary

From invasion by tumor cells, surgical removal of lymph nodes, pressure, or secondary effects of radiant energy

II. Inflammatory

As exemplified by those following filariasis, local infection of the leg, or thrombophlebitis

The precocious type occurs more frequently in girls in a ratio of 4:1, and usually begins between the ages of ten and twenty-four. The cause is entirely unknown. The simple congenital type differs from Milroy's disease only in that there is no history of the disease in the family. The hereditary type is also known as

Clinicopathologic Correlation. Aside from the size, weight, and ungainliness, there are few signs or symptoms of chronic lymphedema. There is no pain, and the disease develops slowly over a period of years. There is, however, a regular complication which is of great interest. In most patients, regardless of the type, there are repeated attacks of streptococcal cellulitis. Within a period of a few hours the entire leg becomes swollen, red, but not particularly painful. There are few systemic symptoms; despite the profound inflammatory reaction, death is rare, and the condi-

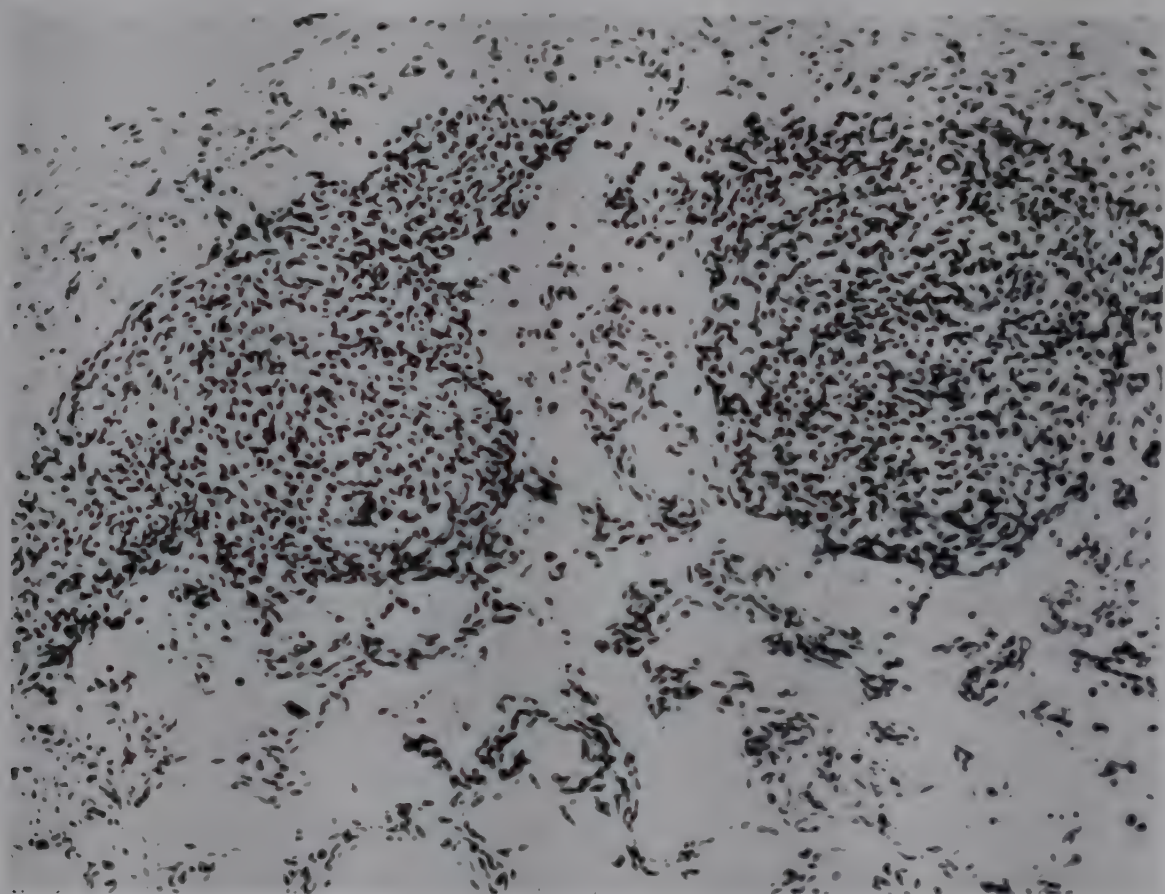


Fig. 389. Cystic lymphangioma of the neck.

“Meige's disease,” or “trophedema.” According to the original description by Milroy, the disease is present at birth, but there are many reports in the literature under this title in which the condition did not develop until many years after birth.

Experimental Chronic Lymphedema. The repeated injection of a suspension of silica in a solution of quinine into the lymphatic vessels of the lower extremity of the dog eventually leads to occlusion, and the complete clinical and pathologic picture of chronic lymphedema. In the subcutaneous tissues there are overgrowth of connective tissue, and dilatation and thickening of the lymphatic capillaries. The protein content of the fluid varies from 4 to 5 per cent (Drinker, Field, and Homans).

tion subsides in from three to seven days. There has been a tendency to regard this inflammatory process as the cause of the chronic lymphedema, but the fact that dogs with the condition also frequently develop streptococcal cellulitis would indicate that these repeated inflammatory states are the result and not the cause of the blockage of the lymphatic vessels.

Cystic Lymphangioma

Cystic lymphangiomas occur in the neck and in the inguinal region. The usual name applied is “cystic hygroma.” The word “lymphangioma” designates a specific histogenetic type and is decidedly preferable.

Pathologic Anatomy. The tumors vary from a few small cysts to large masses, ex-

panding the neck and invading the thoracic wall and the upper arms. On dissection numerous small and large, thin-walled cysts, filled with a clear straw-colored or colorless fluid, are seen. Some of the cysts may communicate with one another, but most of them are independent, closed cavities. Between the cysts there is a small amount of fibrous tissue, in which the normal structures of that region are compressed and atrophic. In the walls of the cyst and in the connective tissue there are small masses of lymphoid tissue.

Microscopically, the cysts are seen to be lined with a flattened endothelium which rests upon a moderately collagenous connective tissue. About the edges of many cysts there are small, solid or hollow evaginations which extend into the surrounding tissue. Mitotic figures are rare. Skeletal muscle fibers and other structures trapped between the cysts show advanced atrophy. Chemical examination of the fluid shows it to contain only a small amount of protein, but a large amount of cholesterol. Study of the sediment in the fluid shows desquamated endothelium and a few white and red blood cells.

Histogenesis. According to Sabin, the lymphatic vessels first appear as outgrowths from the primitive jugular bulbs and from the great veins in the region of the groin. These evaginations lose their connection with the primitive venous system and only later, after many lymph vessels have developed, establish a secondary connection with the jugular vein. In view of the fact that the cystic lymphangioma occurs almost exclusively in the region of the neck and of the groin, it is highly probable that this tumor originates from some anomaly in the development of the primitive lymphatic spaces.

Complications. Secondary infection of the cyst is not an uncommon complication, either from a respiratory infection, or from attempts at surgical removal. In some cases the infection destroys the endothelial lining, fluid is no longer formed, and the cysts undergo regression.

Incidence. Cystic lymphangiomas are commoner in children than in adults, but cases

have been reported appearing as late as thirty-five years of age. It is slightly commoner in girls than in boys, and on the right side than on the left side.

Clinicopathologic Correlation. There are few specific symptoms beyond the mass in the neck. Occasionally, the cysts cause compression of the trachea, with dyspnea; of the esophagus, with dysphagia; and of the nerves and blood vessels, with the usual symptoms resulting from pressure on these structures: hyperesthesia, paresthesia, loss of sensation, and paralysis (Goetsch).

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XCIII

Diseases of the Erythropoietic Tissue

The ultimate function of the erythropoietic tissue is the replenishment of red blood cells destroyed in the natural course of events or by disease. In the normal animal the discharge of adult red blood cells is delicately balanced so that a constant number are maintained in the circulation. If an increased number of red cells are present the condition is known as polycythemia, and is produced either by an accelerated formation and liberation or by concentration in the blood. If a decreased number of red cells are present in the blood, the condition is known as anemia and results from a loss of blood, an increased rate of destruction of red cells, or decreased formation of red cells.

Polycythemia

Polycythemia is an increase in the relative or absolute number of circulating red blood cells. It is customary to distinguish two varieties: primary and secondary. Secondary polycythemia may be a transient state produced by such factors as shock or dehydration following excessive loss or insufficient intake of fluid. In these conditions the increase in red blood cell mass is therefore only a relative one. Secondary polycythemia with actual increase in red cell mass, i.e., absolute polycythemia, occurs transiently in the newly born and chronically in congenital heart disease. The decreased gaseous exchange in the more common chronic pulmonary and cardiac diseases also may increase the red blood cell mass but usually not to a degree comparable to that of congenital heart disease or of primary polycythemia. Some chemicals, notably certain coal tar derivatives causing sulfhemoglobinemia or methemoglobinemia, arsenic, phosphorus, and carbon monoxide, may initiate temporary polycythemias as may

the decreased oxygen tension of life at high altitudes. The injection of epinephrine may produce a transient polycythemia, apparently by contraction of the spleen with extrusion of stored red blood cells.

Pathologic Anatomy. The marrow of all the bones in polycythemia vera (primary polycythemia) is hyperplastic, appearing red and fleshy in the gross. Microscopically, both myeloid and erythroid components are increased, and the proportion between erythroblastic and myeloid cells including megakaryocytes is normal. This general hyperplasia may be distinguished from the virtually pure erythroblastic hyperplasia occurring in secondary polycythemia of high altitudes (Merino and Reynafarje), and in other erythrocytoses. The spleen is usually enlarged and averages 700 gm. Microscopic examination reveals an increase in fibrous tissue of the pulp but no characteristic change. Leukopoietic foci are infrequently present in liver, spleen, and/or lymph nodes. Occasionally there is cirrhosis of the liver, possibly primary, but more probably the result of occlusion of the portal or hepatic vein. Enlargement of the liver may accompany thrombosis of the portal vein. There is general engorgement of the organs and frequently hemorrhages and/or multiple thrombi.

An unusual variant of myeloid leukemia may simulate polycythemia vera, eventually revealing its true nature by assuming a more conventional pattern of leukemia (Butcher, Meek, and Custer). Polycythemia vera may possibly, but rarely, terminate as myeloid leukemia.

Incidence. Primary polycythemia, known also as Vaquez-Osler's disease or erythremia, occurs in all parts of the world, developing usually between thirty-five and fifty years although the deep red color of the skin may

have been present for years. About half of the patients are Jewish.

Etiology. There is no established cause of polycythemia vera. The demonstration of thickening of the blood vessels, especially the capillaries, in the bone marrow (Reznikoff, Foot, and Bethea) is the sole support of the thesis that local hypoxia may stimulate red blood cell formation to abnormal limits. Present methods have failed to detect differences in oxygen concentration in bone marrow in normal persons, anemic patients, and patients with erythremia to prove or disprove such a theory (Berk, Burchenal, Wood, and Castle; Wasserman, Dobson, and Lawrence). Evidence against bone marrow hypoxia as a cause of increased erythropoiesis is the fact that in tissue culture the red blood cell progenitors grow well in the presence of 50 per cent oxygen and poorly under reduced oxygen tension (Rosin and Rachmilewitz), and that oxygen saturation and tension of bone marrow blood fall for only a few hours after severe hemorrhage in dogs, returning to normal for the entire regenerative period which follows (Grant and Root).

Clinicopathologic Correlation. The basal metabolic rate is usually elevated, not necessarily proportional to the increased red and white blood cell count. There is a decrease in the minute-volume output of the heart, probably related to the increased viscosity of the blood. Apparently the coefficient of oxygen utilization is low, despite the fact that the oxygen saturation of the arterial blood is normal (Wasserman, Dobson, and Lawrence) except possibly after exercise (Harrop and Heath). This is in contrast with the unsaturation of the arterial blood at all times in secondary polycythemia of congenital heart disease. All of these factors bring about an inability to regulate the surface temperature. Gout occurs in about 5 per cent of cases as a result of the hyperuricemia which is due to catabolism of nucleoprotein from extruded nuclei of maturing normoblasts. Hemostasis with hypoxia of the tissues probably accounts for the protean manifestations of polycythemia vera including the neurologic findings, impaired hepatic function, and tendency toward esophageal varices and peptic ulcer with hemorrhage. The increased number of cells is responsible for the color of the skin and mucous

membranes. Radioactive phosphorus is useful in treatment.

Anemia in General

Anemia may be defined as a decrease in the concentration of the red blood cells, of hemoglobin, or of both, in the circulating blood. It is caused by a failure of the hemopoietic organs to compensate for blood loss or destruction. It may occur either as a result of an abnormal loss or destruction of blood, surpassing the utmost powers of the blood-forming organs, or as a result of abnormal decrease in the rate of blood production. Often both of these factors contribute to the production of anemia. It follows from the preceding definition of anemia that the peripheral blood does not always reflect the state of the bone marrow. As stated previously, in pernicious anemia there may be a decrease of circulating red blood cells to less than one million but examination of the bone marrow shows hyperplasia of the erythropoietic tissues. In contrast, in aplastic anemia, a reduction in the circulating red blood cells is associated with an almost complete absence of erythropoietic tissue in the bone marrow.

Types of Anemia. It is customary to divide anemia on the basis of the size of the red blood cell into microcytic, normocytic, and macrocytic; and on the basis of the hemoglobin content of each red blood cell into hypochromic, normochromic, and hyperchromic. The microcytic and hypochromic types are usually associated, as are the macrocytic and the hyperchromic.

Classification of the Anemias. In some instances precise knowledge is available concerning the cause of anemia, but in many others the cause is still unknown. Any classification then must be based upon anatomic or clinical grounds. The following classification, proposed by Castle, seems satisfactory:

- (A) Anemia mainly due to loss of blood or increased destruction of blood (bone marrow physiologically hyperactive)
 - I. Anemia from loss of blood as in acute hemorrhage
 - II. Anemia from increased destruction of blood
 - (a) From extrinsic causes, as toxins of bacteria and chemical substances: lead, nitro-compounds, etc. (p. 804)

- (b) From intrinsic causes
 1. Associated with abnormal red blood cells—congenital hemolytic anemia, paroxysmal nocturnal hemoglobinuria, sickle cell anemia, and erythroblastic anemia (p. 577)
 2. Resulting from hemolysis—transfusion reactions, paroxysmal hemoglobinuria
- (B) Anemia mainly due to decreased blood production (bone marrow physiologically hypo-active)
 - I. Nutritional deficiency of the blood-forming organs
 - (a) Deficiency of substances effective in Addisonian pernicious anemia—pernicious anemia, macrocytic anemia associated with sprue, pregnancy, and pellagra, and macrocytic anemias resulting from pathologic conditions of the gastro-intestinal tract (see p. 557)
 - (b) Associated with a deficiency of iron and other substances concerned with the production of hemoglobin—hypochromic anemia of infancy and childhood, chlorosis, hypochromic anemia

- associated with pregnancy and lesions of the gastro-intestinal tract, and chronic hypochromic anemia
- II. Anemia related to deficiency of the endocrine glands, notably the thyroid and pituitary
- III. Anemia resulting from toxic inhibition of the blood-forming organs
 - (a) From poisons of external origin, as benzene, arsphenamine, and compounds of gold
 - (b) From toxins of internal origin, as in chronic infections and in chronic uremia
- IV. Anemia from physical injury of the blood-forming tissues, as by radiant energy
- V. Anemia associated with mechanical interference with the blood-forming organs, such as replacement of the bone marrow with leukemic cells, Hodgkin's disease, primary or metastatic tumors of the bone, and osteosclerosis
- VI. Idiopathic anemias—congenital anemias of infants, aplastic anemia, and splenic anemia (Banti's disease).

Anemias from Increased Blood Destruction

FROM EXTRINSIC CAUSES

There is an endless list of substances which in some instances may exert deleterious effects on the circulating erythrocyte, either by producing hemolysis or by rendering the cell ineffective for the transport of oxygen. Some of these agents may in other instances affect the bone marrow directly (see hypoplastic and aplastic anemia).

Pathologic Anatomy. The red bone marrow is increased, replacing part of the fatty marrow, because of erythropoietic hyperplasia in which normoblasts predominate. The liver and spleen are usually enlarged, the size depending on the duration and severity of the red cell destruction and upon the number of foci of compensatory erythropoiesis. The spleen may return to normal size following recovery from the anemia. Individual erythropoietic cells do not usually show abnormalities although the circulating erythrocytes may exhibit degenerative effects of the toxic substance, e.g., the basophilic stippling characteristic of chronic lead poisoning. Reticulocytes are greatly increased and an occasional normoblast may appear in the peripheral blood.

Clinicopathologic Correlation. The general

effects of anemia will be found in the various organs and tissues as well as more specific lesions characteristic of individual toxic agents, for example, the infarcts of subacute bacterial endocarditis, the wrist drop or encephalopathy of lead poisoning, and liver damage coincident with the anemia of hydrogen arsenide intoxication. Acetanilid poisoning usually causes cyanosis due to the formation of methemoglobin or other pigments. In conditions where hemolysis is acute and severe, and especially if shock occurs, there is the possibility of hypoxic nephrosis (p. 738), with dark scanty urine and evidence of renal damage.

FROM INTRINSIC CAUSES

Sickle Cell Anemia. From 5 to 9 per cent of all Negroes inherit an anomaly of the erythrocyte consisting of a capacity to assume multipointed, bizarre forms when placed in a decreased oxygen tension. This tendency to sickling is inherent in the cell and becomes more pronounced as the cells age. The erythrocytes have an increased resistance to hypotonic solutions but a decreased resistance to

mechanical destruction. The demonstration of sickle cells in a member of any race suggests an admixture of Negro blood in the immediate or remote ancestry (Ogden). About 2.5 per cent of persons with the sickling trait (sicklelemlia) develop sickle cell anemia (Diggs, Ahmann, and Bibb).

Pathologic Anatomy. The alterations in the tissue in sickle cell anemia are related to capillary stasis, increased liability to thrombosis, and increased destruction of red blood cells (Diggs and Ching). The skin and mu-

the sinuses which permits the free escape of blood into the pulp. This results in the formations of pools in the intermediate pulp, and the eventual fibrosis in this region (Rich). The kidneys are hyperemic and pigmented with hemosiderin. The bone marrow in a well developed example of the disease is richly cellular, particularly with normoblasts as well as reticulo-endothelial cells containing hemosiderin. Occasionally foci of necrosis occur and fat embolism from this source has been reported (Wade and Stevenson). There is at

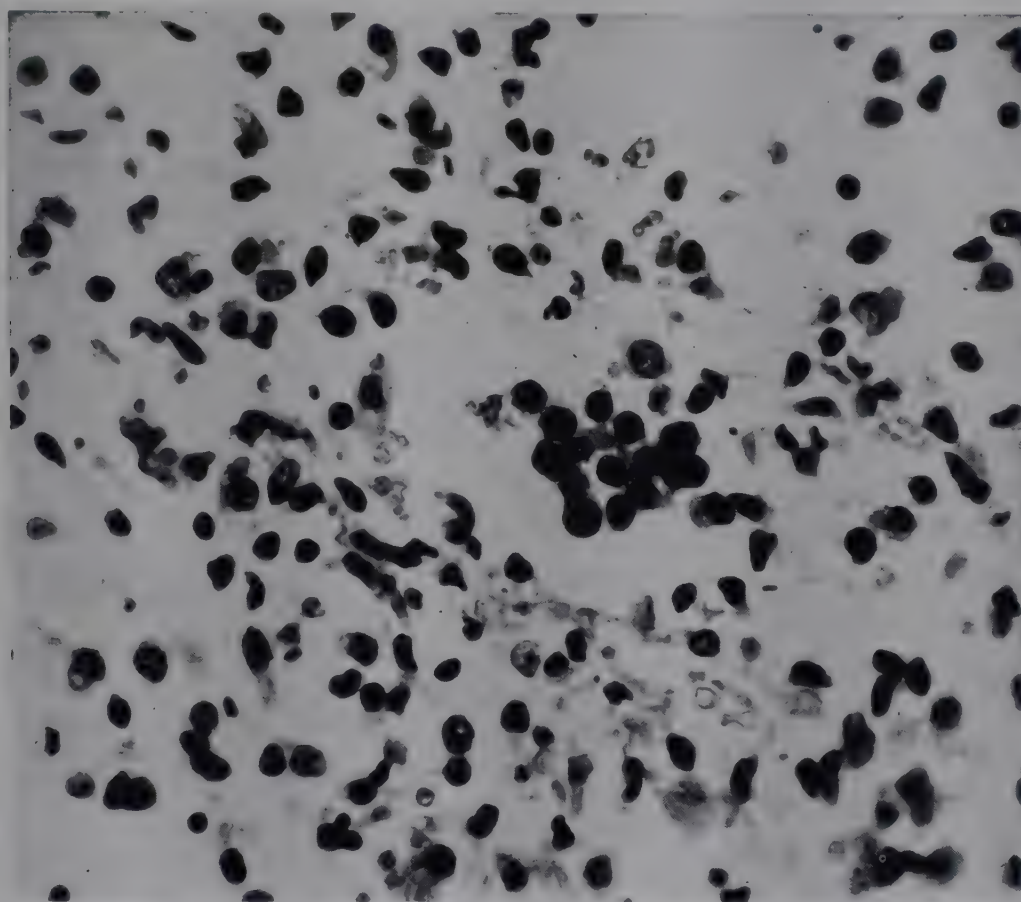


Fig. 390. Extramedullary erythropoiesis in the spleen.

cous membranes are pale, and the lymph nodes moderately enlarged. Chronic ulcers or scars of the legs are present in three of every four adults with the disease. These ulcers have no distinctive features except for the capillaries which are congested with sickle cells. The heart is dilated, frequently enlarged, and pale. Fatty degeneration and focal fibrosis are evident microscopically. The liver is large, firm, and dark reddish brown. The capillaries are distended and Kupffer cells are conspicuous because of hyperplasia and phagocytosis of sickle cells with formation of hemosiderin. In the early stage, the spleen is slightly enlarged, while in the terminal stage it is small, fibrotic, and rich in deposits of altered blood pigment. In both sicklelemlia and sickle cell anemia the spleen shows a malformation of

times thrombosis of small vessels with infarction in the brain, spleen, and kidneys. (Connell). In cerebral vessels there may be in addition an obliterative endarteritis (Bridgers). In persons with sicklelemlia the only constant change in the tissue is the lesion of the spleen.

Clinicopathologic Correlation. The increased destruction of the abnormal red blood cells is reflected in an alteration in the metabolism of pigments. There is urobilin but no bilirubin in the urine. The direct van den Bergh reaction is delayed and the excretion of pigment by the liver is increased. The increased metabolism of biliary pigment promotes a tendency to gallstones of the pigment type. The signs and symptoms in sickle cell anemia are those of anemia—weakness, fatigability, and paleness of the tissues—and of

vascular occlusion with infarcts in the spleen, brain, and kidneys. Effects on the heart include enlargement, appearance of murmurs, and prolongation of the P-R interval (Klinefelter). The administration of pure oxygen will decrease the percentage of sickle cells in the blood (Reinhard, Moore, Dubach, and Wade) and decrease erythropoiesis in the bone marrow.

In children the protean manifestations include fever and vague pains which have been misinterpreted as those of acute appendicitis, meningitis, rheumatic fever, or other diseases. The disease does not ordinarily manifest itself in the newly born presumably because of a difference between the red blood cells formed after birth and those generated in the fetus (Watson).

Elliptocytosis. A small percentage of red blood cells in most persons are elliptical or rod shaped. During the course of many anemias, regardless of the cause, the number of these abnormally shaped cells is materially increased. On the other hand, in members of a few families in various parts of the world over 25 per cent of the red blood cells have this characteristic shape. The tendency is inherited as a mendelian dominant and is apparently slight at birth. Ovalocytes increase in the postnatal period to reach a constant percentage at about four months of age (Helz and Menten). In sealed fresh blood preparations the cells do not assume an elliptical shape. In fact, they may become spherical and lose their central pallor under such conditions (Wagner). Histologic study of the bone marrow shows no abnormality and erythropoiesis is entirely normal. Pathologic changes in the other viscera are unknown (Wyandt, Bancroft, and Winship). A small percentage of persons with elliptocytosis have an associated anemia, jaundice, or splenomegaly. The preponderance of evidence indicates that this is coincidence.

Hemolytic Anemia. Hemolytic Jaundice. The terms "hemolytic anemia" and "hemolytic jaundice" are interchangeable and the selection of one depends on which of the two changes resulting from an abnormal destruction of red blood cells is to be emphasized. The basic concept of hemolytic jaundice was set forth by Hayem in 1898 and by Minkowski in 1900. Between 1907 and 1914 Widal

and others published observations on a similar disease process. From these observations two types of jaundice have been delineated: a congenital type, of Hayem and Minkowski, and an acquired type, of Widal. In both, there are recognized acute, subacute, and chronic varieties; the congenital type also has latent intervals. The following classification of Dameshek and Schwartz seems most satisfactory:

- (A) Congenital hemolytic jaundice (anemia)
- (B) Acquired hemolytic jaundice (anemia)
 1. Secondary to known cause (infections, chemical, "toxic," pregnancy, etc.)
 2. Symptomatic, in association with certain, usually primary diseases, as lymphatic leukemia, Hodgkin's disease, carcinomatosis
 3. Of unknown cause, with or without hemolysis in the serum.

Pathologic Anatomy. The congenital and acquired varieties of hemolytic jaundice present identical pathologic changes. The spleen is greatly enlarged, and weighs 1000 to 1500 gm. The capsule may be slightly thickened but adhesions to the surrounding peritoneum are not excessive. The cut surface is dark purplish red, and homogeneous in texture. The malpighian bodies are small and sparsely distributed. The sinusoids are widely dilated and are lined by cuboidal cells. The pulp is filled with red blood cells while the sinusoids are relatively empty. During hemolytic crises changes in the spleen are more striking. Stagnation and sequestration of the red blood cells with evidence of disintegration have been observed (von Haam and Awny). There is also an increase in reticulo-endothelial cells. The bone marrow is red and exhibits erythropoietic hyperplasia. Normoblasts predominate and tend to be a little larger than normal. When hemolysis is severe, there may be retardation of complete nuclear pyknosis and the nucleus of almost mature cells with polychromatic cytoplasm may be slightly more "open" than in normal normoblasts (Dacie and White). Occasionally the hyperplasia of the bone marrow in the chronic disease causes enlargement of the bones, especially of the skull, with deposition of perpendicular trabeculae on the surface resulting in a "hair-on-end" appearance in x-ray pictures (Cooper). In the liver, kidneys, and lymph nodes there is slight to moderate hemosiderosis, and small

foci of extramedullary hemopoiesis. The gallstones in patients with hemolytic anemia are usually single, rarely numerous, and consist mainly of bilirubin.

Congenital Hemolytic Jaundice (Chronic Acholuric Jaundice; Chronic Familial Jaundice). Congenital hemolytic jaundice is transmitted as a mendelian dominant characteristic, occurs in both sexes, predominantly in the white race, and has been recognized as early as infancy. The disease usually appears before adult life and shows clinical manifestations of anemia, mild jaundice due to increased blood destruction, enlarged spleen, and sometimes gallstones. Invariably, most of the circulating red blood cells are small, spherical cells, easily hemolyzed by hypotonic saline solution. However, 10 to 20 per cent or more of the red cells are reticulocytes which are normal large, tough cells. The "microspherocytosis" is a change which takes place after the erythrocytes have been delivered from the bone marrow. It seems probable that the hemolytic process is associated with a stagnation of red cells in the sinuses of the spleen. Lysolecithin, found normally in the spleen, is possibly formed in concentration sufficient to cause permanent damage to the red cells. The distended condition of the spherocytes facilitates hemolysis either by reticulo-endothelial cells of the spleen or by mechanical action of the circulation (Shen, Castle, and Fleming).

It has been observed that normal red blood cells transfused into patients with congenital hemolytic jaundice live twenty to fifty days, whereas washed cells from these patients survive 100 to 120 days in a normal individual (Loutit and Mollison).

Splenomegaly, reticulocytosis, hyperbilirubinemia, increased urobilin excretion, and the bone marrow hyperplasia are secondary to the hemolysis.

Acquired Hemolytic Jaundice. As noted in the previous classification, some types of acquired hemolytic jaundice are known to be associated with infectious disease, the ingestion of certain chemical substances, pregnancy, and malignant tumors (Stats, Rosenthal, and Wassermann), notably the lymphoblastomas. When associated with infectious diseases, especially in children, the condition is known as "Lederer's anemia." The criteria for the diagnosis of acquired

hemolytic anemias are: a history of acute or fairly acute onset, rapidly progressing pallor and weakness, signs of anemia with jaundice and splenomegaly; laboratory findings of severe anemia, often described as macrocytic because of the compensatory reticulocytosis, evidence of increased blood destruction, the presence of free hydrochloric acid in gastric secretion, and lack of central nervous system signs or symptoms. Congenital hemolytic jaundice may be ruled out on the following points: in acquired hemolytic jaundice the relatives must be shown to be free of similar disease, however mild; enlarged liver and lymph nodes are more common in the acquired disease; microspherocytosis is absent in 60 per cent of cases of the acquired type; leukopenia with atypical lymphocytes and monocytes occurs in acquired hemolytic jaundice whereas the congenital disease usually presents a normal or elevated leukocyte count. The Coombs' test is positive in the acquired disease. This test utilizes anti-human-globulin rabbit serum to demonstrate the presence of globulin antibodies adsorbed to the surface of the red blood cells in cases of acquired hemolytic anemia (Singer and Motulsky). Finally, splenectomy is recommended treatment in acquired hemolytic jaundice but the results are variable as compared with the usual success in the congenital type.

Clinicoathologic Correlation. The intensity of the jaundice and the dark color of the urine and feces depend upon the hemolysis of erythrocytes with increased excretion of urobilin. Anemia occurs when the bone marrow is unable to replace completely the red blood cells. Enlargement of spleen and lymph nodes is a manifestation of reticulo-endothelial hyperplasia probably due to the basic disease as well as to the additional metabolism of bilirubin. The excessive metabolism of biliary pigments causes the bile to be thick and viscid, leading to the formation of gallstones rich in bilirubin. In severe crises the laboratory demonstration of microcytosis, spherocytosis, and fragility may be partially masked by the presence of numerous reticulocytes which are large, relatively flat and tough cells. In the acquired type of hemolytic jaundice there may be signs and symptoms of the febrile, toxic, neoplastic, or other type of disease which preceded the hemolysis.

Thalassemia. A distinctive familial peculiarity of the red blood cells occurs in racial groups which originally lived around the Mediterranean Sea—Italians, Greeks, and Syrians. Clinical disease exists in two forms: a severe, progressive, and usually fatal anemia, at times without signs or symptoms; and a mild asymptomatic form. The former is designated as thalassemia major and the latter thalassemia minor. Synonyms are Cooley's anemia, Mediterranean anemia, familial erythroblastic anemia, and leptocytosis.

Pathologic Anatomy. All elements in the bone marrow are hyperplastic with a great increase in primitive cells of the erythroid series. The trabeculae of the spongy bone are atrophic and new bone is deposited on the surface. This is especially well developed in the calvarium. The spleen, liver, and lymph nodes are enlarged and contain foci of hemopoiesis of all marrow elements. There are extensive deposits of hemosiderin in the liver, pancreas, kidneys, lymph nodes, and other tissues, but not in the spleen (Whipple and Bradford).

Chemical Aspects. Analyses of the liver, pancreas, and lymph nodes show up to ten times the normal amount of iron.

Incidence. In southern Italian and Sicilian stock thalassemia major occurs in one of 2400 births and thalassemia minor in one of 25 (Valentine and Neel). The mechanism of inheritance is as a simple mendelian dominant through either parent.

Pathogenesis. The red cells are hypochromic, there is a low mean corpuscular volume, there is no response to iron, and there is increased resistance to hemolysis, all of which indicate a basic defect in the metabolism of hemoglobin. The presence of stippled red cells suggests a toxic effect. Evidence of hemolysis in severe types indicates an abnormality of destruction, but splenectomy is of no value. The fact that both thalassemia and the sickle cell syndromes are characterized by abnormally thin red cells—target cells—and by oval red cells suggests a relation between the two (Dameshek).

Clinicopathologic Correlation. Thalassemia major appears as a progressive hypochromic microcytic anemia during the first two years of life and death usually occurs before adolescence. Changes in the bones result in retardation of growth and the appearance of a mongoloid type of facies.

Chronic Hypochromic Anemia

It has been customary to designate all examples of hypochromic anemia without obvious blood loss as "idiopathic hypochromic anemia." As has been pointed out by Carl Moore, our knowledge of the metabolism of iron is so complete that there is no longer any reason to use the term idiopathic. A careful study of the patient will almost always reveal either significant blood loss as in menstruation or pregnancy, and/or poor absorption of iron from the intestine as in deficient diet, achlorhydria, or rapid intestinal motility. Hence the proper terminology is chronic not idiopathic hypochromic anemia.

Pathologic Anatomy. Pathologic changes in the tissues have not been adequately studied to warrant definite statements. The bone marrow undergoes erythropoietic hyperplasia of the "micronormoblastic" type (Bodley Scott). The predominant cells are basophilic and polychromatic normoblasts in which cytoplasmic ripening and hemoglobinization seem to lag behind nuclear condensation. No megablasts are present. In cases with dysphagia, there has been reported hyperkeratinization of the epithelium of the pharynx and atrophy of the underlying muscles. In the stomach there is atrophy of the mucosa and at times a chronic gastritis. The enlarged spleen shows an increase in reticulo-endothelial cells and no fibrosis. Fatty degeneration of the liver, kidneys, and heart occurs frequently, as it does in other anemias.

Incidence. Causal Factors. Pathogenesis. The condition is more common in women in the ratio of 9:1, and is almost limited to the period between thirty-five and fifty years, probably as the result of greater iron depletion during menstruation and childbearing. In addition to the anemia there are abnormalities of the epithelium including atrophy of the tongue, hyperkeratinization of the lining of the oropharynx, atrophy of gastric mucosa, and koilonychia. Paresthesia, experienced by about one-fifth of patients, has not been explained pathologically. However, the picture shows abnormalities of the nervous system, stomach, and bone marrow, which are the tissues involved in pernicious anemia. Further, iron therapy causes a reticulocytosis and cure of the patient.

Clinicopathologic Correlation. The initial

loss, if any, of blood through hemorrhage may exhaust the reserve of iron in the tissues and plasma. However, the main cause of the deficiency is the reduced absorption of iron associated with absence of hydrochloric acid in the gastric juice. The ensuing anemia leads to paleness of the skin and mucous membranes, and to weakness. The dysphagia is inadequately explained. The atrophy of the tongue and other abnormalities of the upper gastrointestinal tract, and the paresthesias, are manifestations of deficiency disease on a basis similar to that in pernicious anemia. The clinical and hematologic findings indicate a retardation of hemoglobinization and cytoplasmic development of the erythrocyte due to an insufficient level of plasma iron.

Dysphagia, koilonychia, and hypochromic anemia are major features of a symptom complex known as Plummer-Vinson syndrome. Its relation to carcinoma of the pharynx is discussed under that subject (p. 643). For further discussion of iron deficiency see Chapter VI.

Hypoplastic Anemia—Aplastic Anemia

Aplastic anemia is correctly defined as that condition in which the erythrocytes and other circulating forms of the blood are greatly decreased because of the hypocellular or acellular state of the hemopoietic tissues. Clinically, this condition may simulate some of the refractory and pseudo-aplastic anemias in which the blood-forming organs may be either normal or hyperplastic (Rhoads and Miller). In most instances the distinction can be made only by examination of the bone marrow. This differentiation is important even though both sometimes qualify for classification among the refractory anemias which do not respond to any form of therapy.

Pathologic Anatomy. The bone marrow in the aplastic anemia is virtually devoid of normal hematopoietic elements although grossly it may be red and appear to be cellular. Actually, the marrow spaces are occupied by fat cells which may be irregularly misshapen in acute cases. A few distorted hematopoietic cells may persist between the fat cells, and interstitial hemorrhage is common. In more chronic cases only plasma cells, lymphocytes, and histiocytes may be demonstrable, the lat-

ter in numbers proportional to the number of blood transfusions given the patient. Excessive cellularity of this type may be interpreted erroneously as normal or hyperplastic marrow by an inexperienced observer. Hemosiderin in the histiocytes and interstices depends upon the initial destruction of blood cells, the amount of transfused blood received by the patient, and upon the erythrophagocytosis, which frequently is conspicuous. An occasional chronic case may exhibit fatty replacement of the marrow early in the course of the disease and a fibrosis later. In aplastic anemia there is no extramedullary hemopoiesis. The other tissues of the body frequently show hemorrhage of varying degree, of greatest importance in the brain and gastrointestinal tract. Severe inflammation of the mouth, pharynx, and respiratory tract is most common. In cases of aplastic anemia due to specifically incriminated substances there may be other evidences of sensitivity, e. g., the dermatitis preceding aplastic anemia in soldiers treated with atabrine (quinacrine) (Custer). Fatty degeneration of heart, liver, and kidneys may be found, as in anemia of any type.

Cause. Aplastic anemia may occur following the administration of or accidental exposure to certain chemical and physical agents. It also occurs in patients from whom no history of such exposure can be elicited. The list of agents known to be toxic to the bone marrow includes benzene, organic arsenicals, bismuth, mercury, colloidal silver, dinitrophenol, trinitrotoluene, hair dyes, sulfonamides, atabrine, tridione and "a hydantoin," and benzoate of estradiol. Although sensitivity may play a part of the etiology of aplastic anemia, the quantity and duration of exposure to the toxic agent is also a major factor. The effects of irradiation of the bone marrow have been recently emphasized (Liebow, Warren, and DeCoursey). Aplastic anemia also occurs apparently as a bone marrow exhaustion due to chronic hemorrhage (Stransky and Quitos).

Clinicopathologic Correlation. The pallor and weakness are due to the lack of hemoglobin in the circulating blood. Hemorrhage, occurring early in many cases, follows thrombocytopenia due to paucity of megakaryocytes although other factors probably play a part in the bleeding. The invariably associated agranulocytosis allows extension of some ordinarily trivial infection. In some instances the

antibiotics conquer the principal invader only to have the patient succumb to a relatively avirulent but antibiotic-resistant bacterium. Evidence of sensitivity to an agent may herald the aplasia of the blood-forming tissues, e. g., the cutaneous lesions which sometimes precede the hematologic changes in atabrine, arsenical, and sulfonamide administration. Fortunately, there is a quantitative factor in the causation of the disease, usually allowing withdrawal of the agent, if it can be identified, with consequent recovery of the patient.

Refractory Anemia

Certain patients suffering from a moderate to severe anemia with no demonstrable cause are not benefited by the administration of the usual stimulants of the bone marrow (liver and iron). Clinically, this set of circumstances has been called "aplastic anemia" by some but recently has more correctly been designated "primary refractory anemia." There are included in this category several conditions which probably will be clarified by current advances in hematology. Refractory anemia is usually not a disease purely of the erythron but shows also a reduction in leukocytes and platelets as conspicuous as the decrease of red blood cells, hence the term "pancytopenia" used by some.

Pathologic Anatomy. On the basis of the appearance of the marrow, five types are recognized. The first is the aplastic or hypoplastic type, in which there is a reduction in the cellularity of the marrow and a relative increase of the immature cells. The second is the normoblastic type, in which the cellularity is normal but in which supravital and histologic studies show a definite suppression of maturation. In the third type, there is hyperplasia of the marrow with a great increase of the most primitive cells—hemocytoblasts. A fourth rare type appears to be a replacement of marrow with megakaryocytes, but without the basic defect of maturation seen in the first three types. In the fifth type, there is fibrosis of the marrow, described elsewhere under the term "myelosclerosis." The gross appearance of the marrow varies from a yellow translucent (aplastic) to a red cellular (hyperplastic) tissue depending on the type (Rhoads and Miller).

Pathologic changes in other tissues are not constant. In an occasional patient there are

no other lesions, and one must conclude that death results from the anemia alone. In others, there are petechiae and ecchymoses, probably related to the thrombocytopenia, and severe necrotizing inflammations of the mouth, pharynx, and respiratory tract, probably related to the granulocytopenia. The heart, liver, and kidneys may show fatty degeneration. All the organs are pale.

Pathogenesis. It is evident, on the basis of the five types outlined, that there are two great categories: those types related to a suppression of maturation (the first three), and those types related to replacement of the bone marrow (the last two). In contrast with other known defects of maturation—pernicious anemia and granulocytopenia—it would appear that refractory anemia results from irreversible damage to the marrow, or from lack of or inability to utilize some unknown maturation factor.

Causal Factors. In many patients, the onset and continued course of refractory anemia may be related to the ingestion of or the exposure to a chemical or physical agent that is known to depress the bone marrow. Remission in a few cases in women following delivery suggests a causal relation of the gravidity (Hurwitt and Field). In other patients, there is no such contributing factor.

Clinicopathologic Correlation. The anemia is responsible for the outstanding symptoms and signs: weakness, fatigability, and pallor. The onset is insidious, and men in early and middle adulthood are most often affected. In keeping with the lack of maturation of all cellular elements of the marrow, there are leukopenia, thrombocytopenia, and a slight increase of normoblasts and reticulocytes. Transfusions may prolong a useful and comfortable life in the less severe types (Thompson, Richter, and Edsall).

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XCIV

Diseases of the Leukopoietic Tissues

Hodgkin in 1832 described seven cases of a disorder affecting the "absorbent glands and spleen." Alterations of the blood cells were not observed although a review of the lymph nodes a century later showed lesions in two cases consistent with the diagnosis of lymphoid leukemia and three cases conforming to the current concept of Hodgkin's disease. Virchow in 1845 first noted that at autopsy certain pathologic changes were associated with a buff or gray colored blood, and he coined the name "leukemia" in his classical papers on "Weisses Blut." Later, two types were recognized, myeloid and lymphoid, on the basis of the type of cell involved. In 1913, a third type, monocytic, was reported. Since then, varieties of leukemia have been described representing virtually every cell of the leukopoietic tissues. Each variety has been regarded as a distinct entity by at least a few observers, the more rare varieties being repeatedly re-discovered.

Soon after Virchow's description of leukemia, Cohnheim recognized at autopsy similar pathologic findings in the viscera, but no apparent change in the blood. He proposed the term "pseudoleukemia," but this has been replaced by "aleukemia" (an obvious etymologic paradox—"White blood that is not white blood") or "subleukemic leukemia."

It was observed that cases of leukemia could, on the basis of duration of life and relative incidence of certain signs and symptoms, be arbitrarily divided into acute and chronic leukemia. Thus it has become conventional to classify the leukemias and related conditions on the basis of several different factors: (1) the presence or absence of an increased number of abnormal cells in the blood: leukemic or aleukemic; (2) the type of cell involved: myeloid, lymphoid, or monocytic, etc.;

and (3) the duration and character of the disease: acute or chronic. The observation of localized nodules or tumors composed of similar cells with or without invasion of the blood necessitates the addition of a fourth factor: the presence or absence of localized tumors.

General Pathologic Changes of Leukemia

The several types of leukemia present a basically similar pathologic picture except for variations which are more quantitative than qualitative. The pattern of each type depends upon changes which may be divided into five categories: (1) increase in the size of organs, (2) presence or absence of localized tumors, (3) destruction or displacement of tissue, (4) hemorrhage, and (5) inflammation.

Increase in Size of Organs. The organs affected most frequently and obviously are the spleen, lymph nodes, liver, and kidneys. The degree of enlargement depends on the cell type and duration of the leukemia. In all there is usually involvement of the liver, so that it weighs 2000 to 3000 gm. The spleen is most conspicuously enlarged in myeloid leukemia, in which it may weigh as much as 5000 gm. (Krumbhaar and Stengel). As in any chronic enlargement of an organ, there is thickening of the capsule so that it becomes white and opaque. There are frequently fine fibrous adhesions to the surrounding serosal surfaces. The lymph nodes display the greatest increase in lymphoid leukemia, but are affected in all types. The nodes develop thickened capsules which become interadherent, but there is rarely fusion of the lymph nodes. In myeloid leukemia the entire bone marrow is gray or grayish yellow and excessively cellular. Both the red and the fatty marrow of

all bones are altered in this generalized disease. In lymphoid and monocytic leukemia the marrow sometimes resembles that of myeloid leukemia. However, some cases of lymphoid leukemia may show only foci of lymphoid replacement of the marrow although the spleen and other viscera are greatly enlarged. Until such foci are excessive in number or become confluent, they are indistinguishable from the foci of lymphocytes found occasionally in normal bone marrow. In the enlarged spleen of leukemia, zones of abnormal white blood cells may elevate the intima of veins and arteries and encircle the intr trabecular arteries (Jaffé). These changes and venous thrombi lead to the infarction which occurs commonly in leukemic spleens. The gross pattern of the liver, spleen, and kidneys is partially or wholly effaced by the "infiltrating" leukemic cells and the pallor of the associated anemia which effect a blending of the various components of the organs.

The replacement of the bone marrow leads to destruction of the normal elements necessary for the formation of granulocytes and erythrocytes. This causes a myelophthisic anemia of varying degree, and any longstanding anemia produces fatty degeneration, particularly of the heart and kidneys. All of the organs of the body are pale, in part due to the anemia and partly because of the gray color of the many leukocytes.

Localized Tumors. The presence of localized tumors is occasionally of assistance in the determination of the type of leukemia. Localized involvement of the skin by the so-called premalignant lesions of mycosis fungoides ultimately develops into plaques or nodules. Some cases of mycosis fungoides eventuate as lymphoid leukemia (Berman) while others terminate as reticulum cell sarcoma or Hodgkin's disease (Montgomery). Small nodules in the skin, called "leukemia cutis," are more common in monocytic leukemia than in the other two main types. Larger tumor nodules in the skin or in the viscera are observed in lymphoid leukemia. These tumor masses are particularly prominent in the superior mediastinum and are more frequently observed in children than adults. When the thymus is replaced by cells of lymphoid leukemia or lymphosarcoma the term "thymoma" has been erroneously employed by some authors. In

such instances there may be an associated myasthenia gravis. Myeloid leukemia with local deposits constitutes the condition known as "chloroma." These deposits are more common in the retro-orbital tissues, producing exophthalmos, and in the periosteum of the long bones. The term "chloroma" stems from the grossly evident greenish gray color attributed to the presence of protoporphyrins (Goodman and Iverson).

Tissue Destruction. In general, the cells of leukemia do not destroy preexistent tissues, but only push them apart. There are, however, exceptions—the chloroma in the retro-orbital tissues may cause resorption of the roof of the orbit with erosion into the cranial cavity. Further, in children the long bones may show expansion of the marrow cavity, atrophy of the cortex, periosteal elevation with new bone formation due to involvement by cells of lymphoid leukemia (Kalayjian, Herbut, and Erf). In advanced myeloid leukemia, the proliferation of cells in the bone marrow may lead to resorption of trabeculae, but rarely of the cortex of the bone. In an occasional case, this resorption of calcium in bone leads to metastatic calcification in the kidney, lungs, and stomach.

Hemorrhage. The manifestations of hemorrhage vary with the type of leukemia, and are far more common in acute leukemia than chronic leukemia. Hemorrhage occurs as petechiae or ecchymoses in the skin, into the lumen of the gastro-intestinal tract, and into the soft fat about the renal pelvis and ureters, and occasionally into the brain, the lung, and the solid viscera. In chronic leukemia, the evidences of hemorrhage are less conspicuous and there is no striking difference between lymphoid and myeloid leukemia except in chloroma, in which hemorrhage is one of the most prominent features of the condition. In general, hemorrhage in the leukemias is associated with a thrombocytopenia resulting from a decrease in number of megakaryocytes in the bone marrow.

Inflammation. Inflammation in a patient with leukemia presents a peculiar problem. The normal mature myeloid cells normally available for defense are, for the most part, lacking. In many of the acute leukemias, especially of the monocytic variety, there are infiltration and ulceration of the gingiva and pharynx, with secondary infection which is

the immediate cause of death. In the lungs, a bronchopneumonia may develop, characterized by the exudation of fluid and fibrin, but the exudate is virtually devoid of cells (Jaffé). The leukemic cell exhibits only slight phagocytic activity for bacteria (Strumia) and antibody formation is frequently defective (Howell). Heterophile antibody increase may follow injections of horse serum in myeloid leukemia but does not occur in lymphoid leukemia (Weinstein and Fitz-Hugh).

Causal Factors in Leukemia

Several facts are known pertaining to the nature of leukemia. Occasionally there is a sequence of some incident and the discovery of leukemia, suggesting a cause-and-effect relationship: acute leukemia in children following an acute infectious disease (Cooke), chronic leukemia in those repeatedly exposed to radiant energy (Ulrich; Henshaw and Hawkins), and leukemia having its onset during the regeneration of the bone marrow after poisoning with benzene and related compounds. Infection as a precipitating or causal factor in leukemia is not widely accepted. Infection is probably merely an incident leading to the examination of the patient and a correct diagnosis. The causal effect of irradiation in leukemia is illustrated by the fact that the disease is 1.7 times as frequent among physicians as it is among males in the general population. Also, the disease is eight to ten times as common among radiologists as among other physicians (March). This relationship appears analogous to the genesis of carcinoma in x-ray or radium burns. Whether the myelofibrosis, myelosclerosis, and myeloid metaplasia in the spleen of humans exposed repeatedly to benzene should be classified as leukemia is a moot question (Heller, Lewi-son, and Palin; Wyatt and Sommers). Whatever the true nature of the condition may be, there is strong evidence that chronic benzene intoxication is an important factor in its genesis (Wyatt and Sommers). It is also interesting that the following agents have produced leukemia in animals under controlled experimental conditions: benzol, indole, methylcholanthrene, and benzpyrene (Furth, 1939). Data pertaining to heredity as a factor in human leukemia are inconclusive (Ardashnikov).

There is some evidence to support three main theories regarding the nature of leukemia. The first, that the hyperplasia is a response to an unidentified infectious agent, has no support from the most exhaustive experiments in mammals, although in birds leukemia is caused by a virus (Furth). The second theory, that it is a metabolic disturbance in which there is excess, deficiency, or abnormal formation of an essential substance, is supported by the relatively low respiration of surviving leukemic cells, unlike that of malignant tumors; and the apparent failure to transmit the disease to other humans. Further, the development of spontaneous leukemia in animals may be inhibited by underfeeding (Saxton, Boon, and Furth). Of interest is the demonstration in the urine of leukemic patients of certain substances which produce leukocytic reactions in experimental animals (Miller and Turner). The significance of these demonstrations is yet to be determined. Facts favoring the third theory, that it is a malignant neoplasm, are: the invariably fatal nature of a disease which follows the same general pathophysiologic laws as do malignant tumors. This behavior applies to both human and experimental leukemia.

Acute Leukemia

Pathologic Anatomy. The pathologic picture at autopsy in acute leukemia is more that of hemorrhage and inflammation than of leukemic infiltration of the organs. The liver, lymph nodes, and spleen are usually only slightly enlarged. There is extensive hemorrhage, most commonly found about the kidneys, in the oropharynx, and in the gastrointestinal tract. The leukemia infiltration of the organs is less advanced than that of chronic leukemia. When extensive leukemic infiltration and enlargement of the organs occur in a clinically acute case, these findings suggest that the case may actually be a sub-clinical chronic leukemia terminating in an acute phase or crisis. It is rarely possible to make a gross diagnosis of the type of leukemia when the disease is acute. Some cases of acute leukemia, particularly in children, defy classification of the cell type beyond "blast cell" leukemia or "stem cell" leukemia. Close histologic studies are usually necessary to distinguish the three main types: acute

myeloid, acute lymphoid, and acute monocytic.

Incidence. Acute leukemia is predominantly a disease of children and young adults, with a sex ratio of 2 to 1 in boys (Cooke). Over 80 per cent of all patients die within two months after the onset of symptoms (Warren).

Clinicopathologic Correlation. The clinical manifestations are principally those of infection and hemorrhage. The hemorrhage is associated with a thrombocytopenia and a de-

Chronic Myeloid Leukemia

The older term, "splenomyelogenous leukemia," indicates that the outstanding changes are in the spleen and bone marrow. The spleen is greatly enlarged and weighs 1000 to 2000 gm. The capsule is usually slightly thickened but may show sectors where leukemic cells have replaced some of its tissue (Jaffé). The splenic substance is a uniform gray-red, and anemic infarcts a few millimeters to several centimeters in diameter are common. These

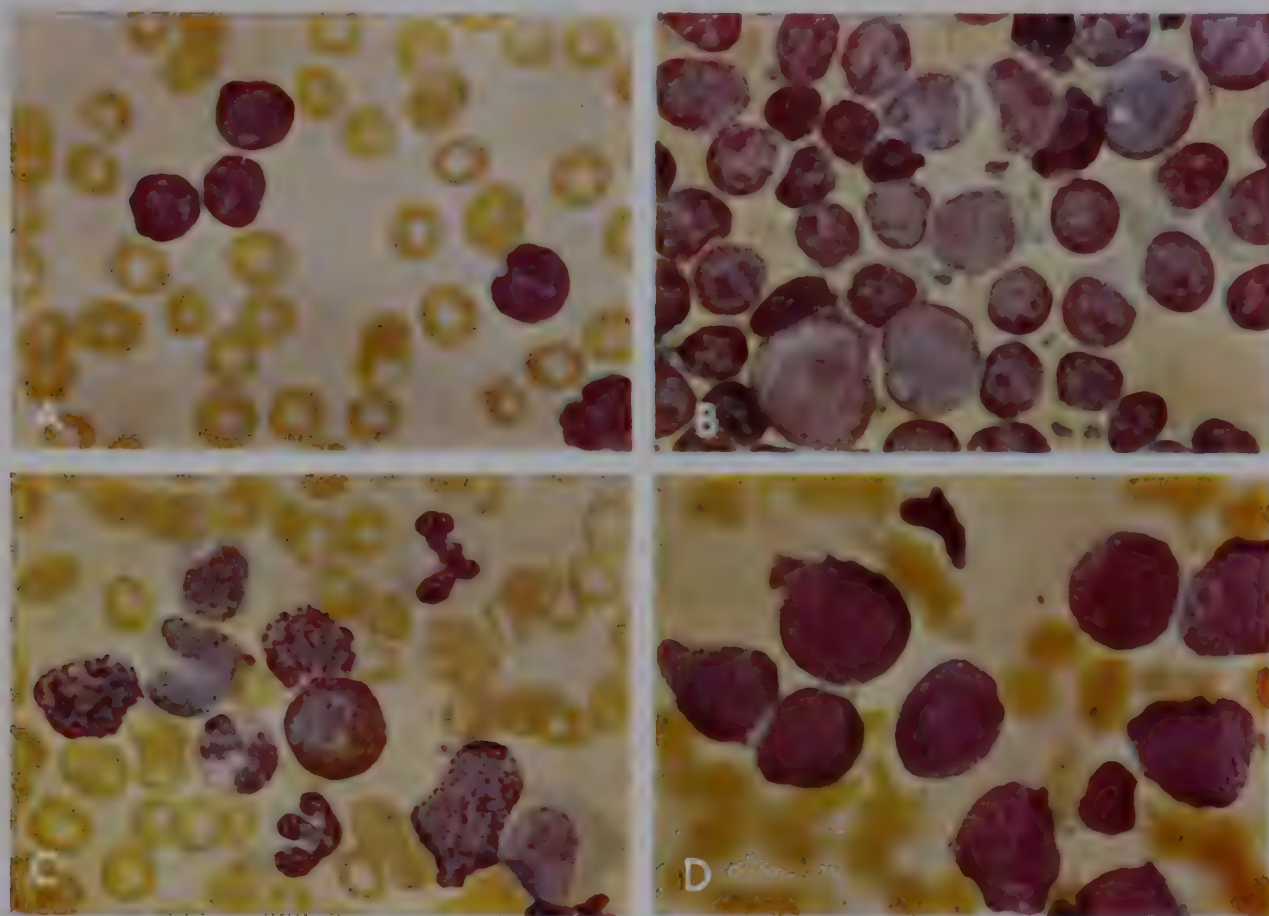


Fig. 391. *A*, Blood in lymphoid leukemia. *B*, Bone marrow in lymphoid leukemia. *C*, Blood in myeloid leukemia. *D*, Bone marrow in myeloid leukemia. (Photographs taken by Dr. Malcolm Cook for Dr. C. V. Moore.)

creased number of megakaryocytes in the bone marrow. The infection is apparently related to alterations of the mechanisms of immune reaction of the body, including decreased phagocytic activity of the polymorphonuclear leukocytes and leukemic cells. Gingival infection and leukemic infiltration are common and may prompt extraction of a tooth. The patient may therefore date his disease from that operative procedure (Warren; Forkner). Acute leukemia mimics a variety of conditions clinically, particularly those diseases presenting slight fever and vague pains and tenderness in muscles and bones (Kalayjian, Herbut, and Erf). The diagnosis of acute leukemia is sometimes exceedingly difficult in the aleukemic form.

are related to leukemic involvement and thrombosis of the intratrabecular veins. The bone marrow of all bones is gray and excessively cellular, with almost complete replacement of the fat as well as the erythropoietic tissue (Fig. 391, *D*). In all parts of the marrow there are myeloid cells corresponding to myeloblasts and myelocytes, although in any one case there is a tendency to uniformity. The lymph nodes are enlarged because of the presence of leukemic cells which, unlike those of lymphoid leukemia, do not usually obliterate the architecture. The liver is frequently enlarged, weighing 2000 to 2500 gm., with conspicuous involvement of the portal spaces and filling of the sinusoids with leukemic cells.

Myelofibrosis. Osteosclerosis. Agnogenic Myeloid Metaplasia. Chronic Nonleukemic Myelosis. This rare type of disease consists of fibrosis of the bone marrow, megakaryocytic and myeloid hyperplasia of the enlarged spleen, liver, lymph nodes, and other tissues, and a leukemic or leukemoid picture in the peripheral blood. There is rarely osteosclerosis also. The variable picture and enigmatic character of the conditions has led to many names and interpretations of the disease, if it is one disease. Some authors believe it to be a

with a solution of sodium hyposulfite. Tumors occur most frequently in the cranial bones about the eyes, and produce unilateral exophthalmos (Fig. 392). Treatment with radiant energy is of value and cures have been reported (Washburn).

Eosinophilocytic Leukemia. Both acute (Stephens) and chronic (Bass) forms of eosinophilocytic leukemia have been reported. This variant of myeloid leukemia is peculiar only because eosinophilic cells predominate. The condition must be carefully distinguished



Fig. 392. Unilateral exophthalmos in chloroma. (Photograph from the files of the Barnard Free Skin and Cancer Hospital.)

variant of leukemia (Butcher, Meek, and Custer; Heller, Lewisohn, and Palin; Churg and Wachstein). Others suggest that the condition may be a chronic bone marrow failure following intoxication from exogenous toxic chemicals (Mallory, Gall, and Brickley), hepatic dysfunction, endocrine abnormalities, blood loss or destruction, and cardiovascular disease (Wyatt and Sommers).

Chloroma. In this variety of myeloid leukemia there are green tumor nodules in the periosteum, bones, and dura mater, and less commonly in the skin and viscera. The condition is more common in boys than girls; the average age of onset is eighteen; and the duration of life rarely exceeds six months. The distinctive color is caused by a protoporphyria (Goodman and Iverson), which fades on exposure to light and air, but can be restored

from parasitic disease, Hodgkin's disease, and familial eosinophilia (Stewart).

Basophilocytic Leukemia. An increase of basophils in the blood and tissues is occasionally found in chronic myeloid leukemia, and it is probable that what is called basophilocytic leukemia is only an exaggeration of this phenomenon (Butcher, Meek, and Custer), but the possibility of basophilocytic leukemia must be admitted (Doan and Reinhart).

Other Variants of Chronic Myeloid Leukemia. Clinically and at autopsy there are variants of chronic myeloid leukemia which have been classified according to the cell predominating in the circulating blood, bone marrow, and other involved organs. Such atypical cases include eosinophilocytic and basophilocytic leukemias, as well as more

rarely encountered conditions classified as erythrocythemic, leuko-erythroblastic, thrombocythemic, and megakaryocytic leukemia (Butcher, Meek, and Custer).

General Features of Malignant Lymphoma

The term "malignant lymphoma" is properly applied to all of the malignant neoplasms primary in the lymph nodes and lymphoid tissue throughout the body. The generally accepted variants of the group are follicular lymphoblastoma, lymphosarcoma, lymphoid leukemia, reticulum cell sarcoma, mycosis

fungoides, and Hodgkin's disease. However, histologic study may be misleading because biopsy ordinarily will not give information regarding peripheral blood involvement, i.e., leukemia (Gall and Mallory). Further, the variants tend to coexist and to transform into other types of malignant lymphoma. This fluidity is caused by change in the type and/or degree of differentiation of the "mesenchymal cells" involved and does not indicate the coexistence or development of a separate disease.

Only about 20 per cent of cases of malignant lymphoma maintain a "pure" type lesion throughout their course. More than half of the cases show two or more types of lesions.

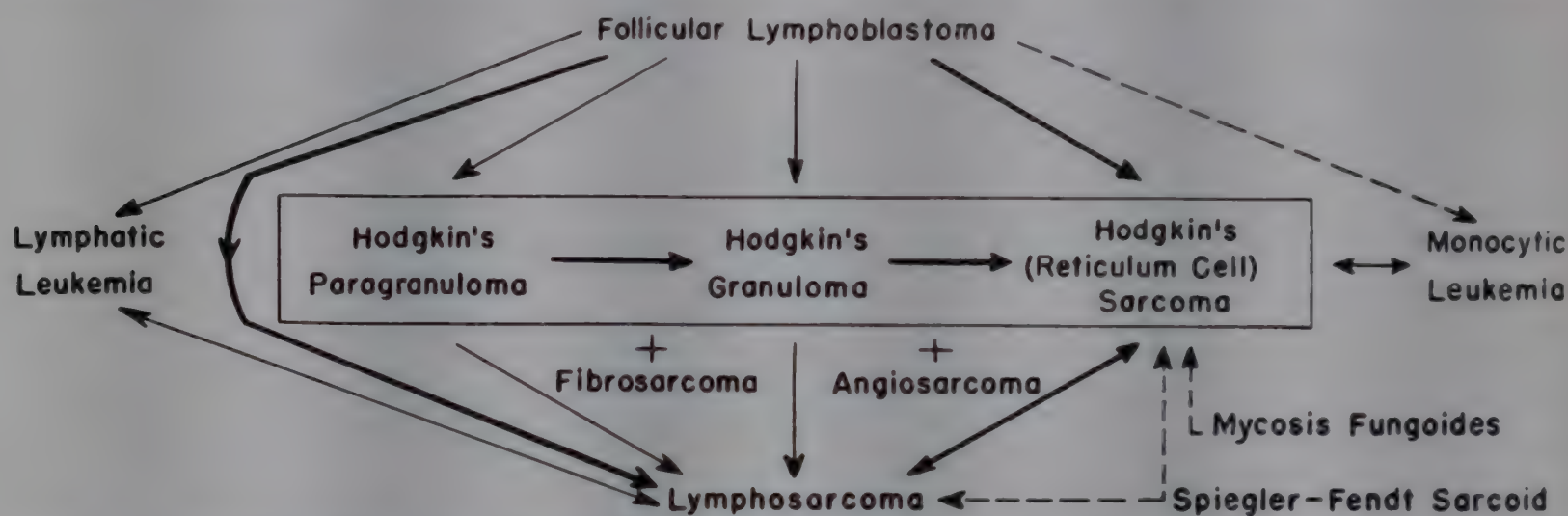


Fig. 393. *Interrelationship of Lymphomas*. The solid lines indicate transitions actually observed in our series in sequential biopsies or between biopsy and autopsy. The heavy lines show the changes most frequently seen, the lighter the more unusual ones. Dotted lines indicate transitions not seen in this particular group of patients, but observed or recorded elsewhere. (From Custer: *An Atlas of the Blood and Bone Marrow*.)

fungoides, and Hodgkin's disease. Custer and Bernhard list monocytic leukemia among these variants of malignant lymphoma, and more recently the rare skin lesion, Spiegler-Fendt sarcoidosis, has also been included (Custer).

Enlarged lymph nodes and spleen are the most constant features of malignant lymphoma. The gross differentiation of the variants of malignant lymphoma is extremely difficult. The size of the affected organs is ordinarily not related to the cell type of the disease but in some cases is proportional to the duration of the disease. The more cellular lesions cause distention of the capsule of the lymph node or other organ and present a dull gray, moderately firm cut surface. The firmest nodes and spleen may be found in Hodgkin's disease when fibrous tissue has replaced the cellular tissue of the earlier phase of the disease. The ultimate diagnosis is a histopathologic problem and depends on the pattern of the lesion and

Approximately 40 per cent of autopsied cases having previous biopsies display a complete alteration of histologic pattern from one type of malignant lymphoma to another (Custer and Bernhard). Figure 393 indicates the transitions from one variant of malignant lymphoma to another as observed among 1300 cases from the Armed Forces Institute of Pathology (Custer and Bernhard).

Malignant lymphoma is more common in males than females in a ratio of approximately 3:1. The variants of the disease exhibit some relation to the age of the patient. For example, chronic lymphoid leukemia is considered a disease of the aged whereas Hodgkin's disease is more common in the young and middle-aged. However, such traits are not invariable and the commendable modern practice of multiple and repeated biopsies in cases of malignant lymphoma may alter the statistics on these variants.

Lymphosarcoma

Lymphosarcoma is that variant of malignant lymphoma in which the primary neoplastic proliferation is in lymphoid tissue.

Pathologic Anatomy. The lymph nodes are enlarged and the capsule is thickened. The lymph nodes may become adherent to one another and form large masses. This is especially true in the cervical and retroperitoneal regions.

14 to 22 microns in diameter with an abundant, eosinophilic cytoplasm and a round or oval, eccentric nucleus without a nucleolus. The lymphoblast is 10 to 20 microns in diameter and possesses a narrow, basophilic rim of cytoplasm about a round or slightly indented, vesicular nucleus. Nucleoli are infrequently observed. The lymphocyte of malignant lymphoma is indistinguishable from the normal lymphocyte, and it is not possible on histologic



Fig. 394. Enlargement of cervical and axillary nodes in lymphosarcoma. (Photograph from files of Barnard Free Skin and Cancer Hospital.)

The tissue bulges from the cut surface and is grayish white and finely granular. The architecture of the node is completely destroyed. Throughout the viscera, liver, spleen, kidneys, lungs, and occasionally in the heart, skin, and other organs, there may be circumscribed nodules of similar tissue.

At least four types of tumors are found: stem cells, clasmatic, lymphoblastic, and lymphocytic lymphoma. In any one tumor one cellular type predominates, but a few of the other cells are found. The stem cell is from 15 to 35 microns in diameter, with abundant, pale-staining, amphophilic cytoplasm, and a large, delicate nucleus and a single, prominent nucleolus. The cells are arranged as solid sheets without clearly discernible cell borders, or as discrete cells with occasional intercellular bridges. The neoplastic clasmatic is from

grounds alone to distinguish between malignant lymphoma composed of the lymphocytic type of cell and chronic lymphoid leukemia.

Incidence. Lymphosarcoma has a sex preponderance of about 3 to 1 in men, and the highest incidence is in the fourth and fifth decades of life. The cause is unknown.

Clinicopathologic Correlation. The average duration of life after the onset of symptoms is about two years. Occasionally lymphosarcoma is a localized disease, and surgical removal is indicated. The outstanding symptoms and signs result from the enlargement of the lymph nodes and of the spleen, the latter of which occurs in about 40 per cent of all cases. The reason for a fever in about a quarter of cases is not evident. In late stages the enlarged lymph nodes may press on blood vessels, nerves, and hollow viscera, and produce ob-

struction with secondary changes (Gall and Mallory; Stout).

Follicular Lymphoblastoma

Pathologic Anatomy. In this condition, known also as "giant follicular lymphoblastoma," "giant follicular hyperplasia," and "Brill-Symmers' disease," the lymph nodes are moderately enlarged, firm, discrete, and normally movable. The capsule is thin and intact. On the cut surface, the greater part of the tis-

tiated from reactive hyperplasia by the absence of phagocytosis, the atypical appearance of the follicular cells, and the obliteration of the sinuses. These are in contrast to the lymph node of benign hyperplasia which shows normal follicular cells, usually including phagocytes, and visible sinuses, sometimes with hyperplastic reticulo-endothelial cells.

In the phase of transition of follicular lymphoblastoma to another variant of malignant lymphoma, the follicular pattern may be discernible only by gross examination of the

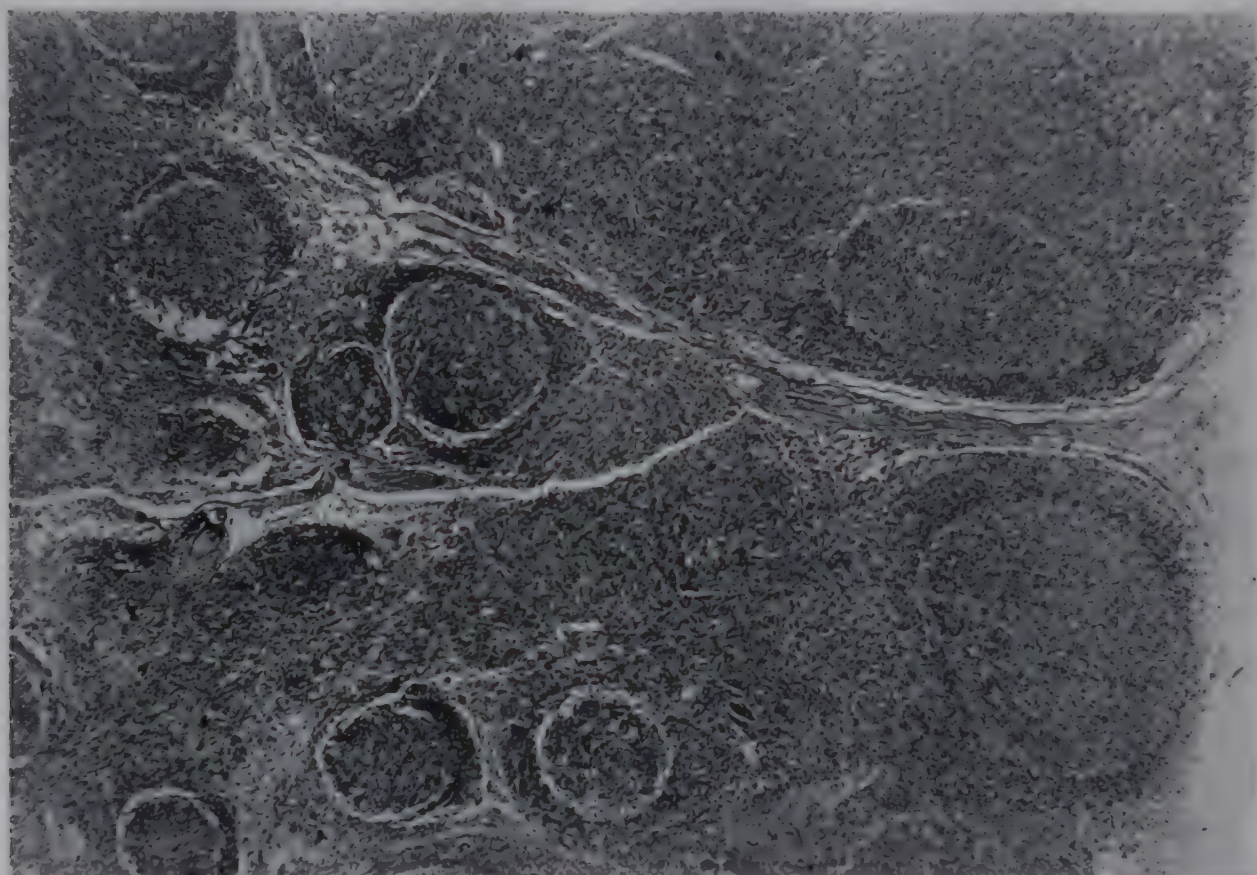


Fig. 395. Giant follicular lymphoblastoma.

sue is occupied by many roughly round, gray or grayish white areas which are the gross expression of a numerical and usually dimensional increase in the primary follicles. The follicles consist of closely packed, moderately large, lymphoblastic cells. An important diagnostic point is the absence of phagocytes among these cells. There are a few mitotic figures. About each germinal center the lymphocytes are compressed into concentrically arranged zones which in some instances are interrupted by confluence of enlarged follicles. The sinuses are inconspicuous. The spleen is enlarged, averaging 1600 gm. The thickened capsule may be attached to surrounding viscera by fibrous adhesions. Grossly and microscopically the appearance of the spleen is essentially the same as that of the lymph nodes. Follicular lymphoblastoma is to be differen-

microscopic section or by use of the inverted ocular of the microscope. The fading follicles may appear as many dense, poorly defined aggregates of lymphocytes or lymphoblasts blending with cells of the scant interfollicular tissue, leading to effacement of lymph node architecture and a fairly monotonous and purposeless distribution of the neoplastic cells. This transition may be detected in lymphosarcoma and Hodgkin's disease not infrequently by use of low magnification (Custer and Bernhard).

Causal Factors. Incidence. The cause of malignant lymphoma including this variant is entirely unknown. The average age of onset is about forty years, and there are relatively few cases in persons less than thirty years old. It is more common in men than women in a ratio of about 2:1.

Clinicopathologic Correlation. Clinically the lymph nodes are discrete, movable, painless enlargements. The cervical lymph nodes are most frequently affected. The liver is occasionally enlarged owing to an increase in the mass of lymphoid tissue. An explanation for the frequent effusions into the serous cavities is not apparent. The average course of the disease is about four or five years, but cases in which the patient survived as long as seventeen years have been described. During the early stages, the lymph nodes are more radiosensitive than any other tissue or tumor in the

malignant lymphocytes in the circulating blood to distinguish it from another variant, lymphosarcoma.

Pathologic Anatomy. The most prominent alterations in chronic lymphoid leukemia are in the lymph nodes, spleen, liver, and bone marrow. The lymph nodes are enlarged sometimes to as much as 4 or 5 cm. in diameter. The capsules are tense but they do not fuse with one another. The substance bulges from beneath the capsule and is grayish white and finely granular. The architecture of the node is completely effaced because of a monotonous

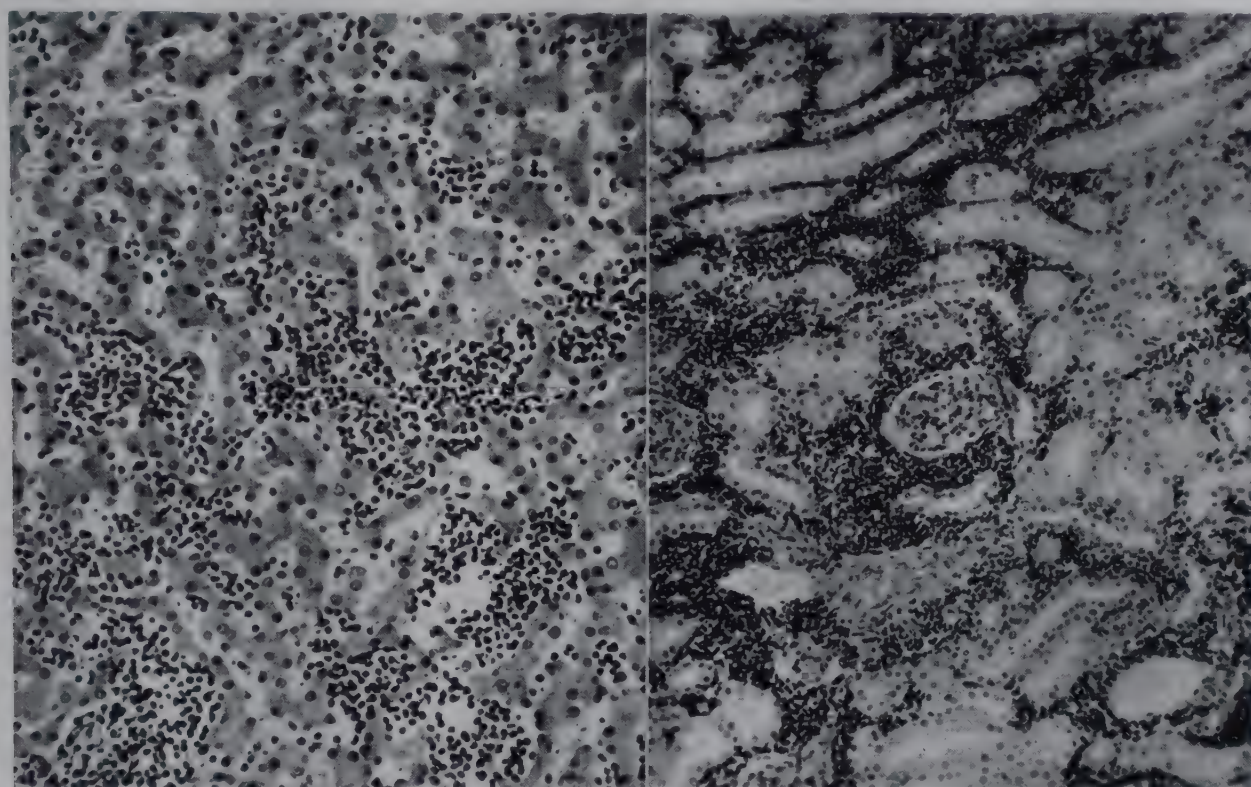


Fig. 396. Lymphoid leukemia. Infiltration in liver and kidney.

human organism (Baggenstoss and Heck). After transition into another variant of malignant lymphoma the susceptibility to irradiation follows that of the particular variant, including tendencies to the so-called "irradiation-fast" state.

Brill, Baehr, and Rosenthal, who originally studied the condition, believed it was benign. Subsequent study of these same patients and of others, however, leaves no doubt that in most patients with follicular lymphoblastoma, the so-called "malignant" condition of the lymph node develops, i.e., the true nature of the disease manifests itself by a transition into some other variant of malignant lymphoma.

Chronic Lymphoid Leukemia

Chronic lymphoid leukemia is one of the variants of malignant lymphoma and shows

overgrowth of leukemic cells which in many cases are indistinguishable from normal mature lymphocytes. The spleen averages 600 to 800 gm. in weight. The capsule is not thickened; the substance is moderately firm and gray. In both the red and white pulp are many diffusely distributed leukemic cells. The liver is enlarged and the neoplastic cells are present in the portal spaces and in the sinusoids of the lobules. The bone marrow may be involved initially by leukemic cells arranged in microscopic nodules which eventually coalesce to present a diffuse grayness grossly. In the advanced disease the fatty and cellular marrow is completely replaced by leukemic cells. The kidneys are frequently large and pale, and the interstitial tissue is infiltrated. A common site of hemorrhage in leukemia is in the peripelvic fibro-adipose tissue, with rupture into the pelvis and consequent hematuria. The gastro-in-

testinal tract may display focal or diffuse tumor masses composed of leukemic cells. This type of lesion is most common in the subleukemic variety of chronic lymphoid leukemia and is one of the most common tumors of the small intestine. The condition has been called "gastro-intestinal pseudoleukemia" (Pearson, Stasney, and Pizzolato). Less frequent sites involved by the disease are brain (Leidler and Russell), bladder, prostate, testes, pleura, lungs, and skin. Cutaneous lesions are not uncommon in chronic lymphoid leukemia but are

leukosarcoma, emphasizes the fluidity in malignant lymphoma, of which it is merely a variant (Custer and Bernhard).

Hodgkin's Disease

It is now over one hundred years since Thomas Hodgkin, pathologist at Guy's Hospital, London, reported on "some morbid appearances of the absorbent glands and spleen." In this century little progress has been made in the understanding of the nature of the condi-

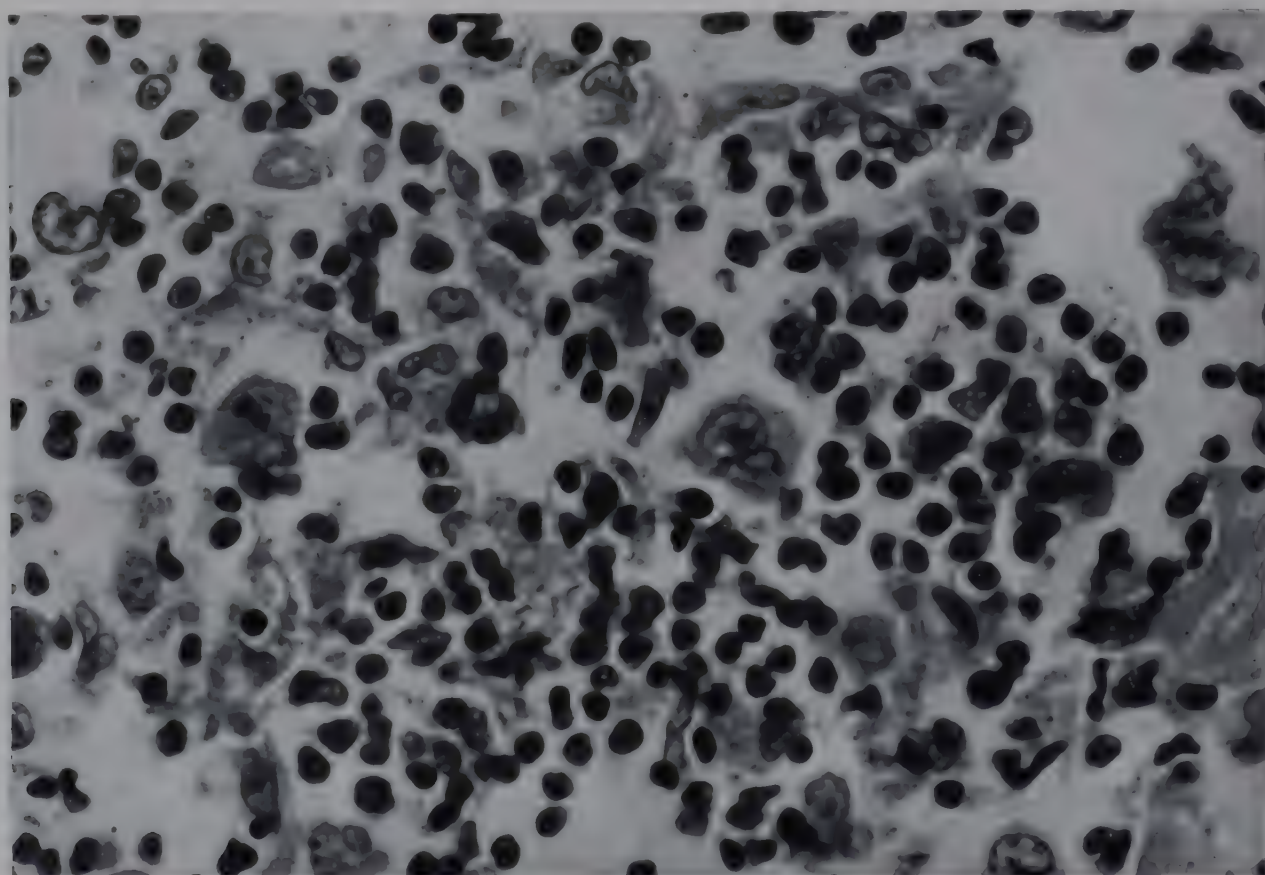


Fig. 397. Hodgkin's disease of lymph node.

usually of the leukemoid variety or are hemorrhages associated with thrombopenia (Epstein and MacEachern).

Thymoma and Lymphoid Leukemia. In most cases of leukemia there is involution of the thymus but there may be tumor formation in the thymus as a part of lymphoid leukemia or the variant, leukosarcoma.

Leukosarcoma. The term "leukosarcoma" was first used by Sternberg to designate a condition in which there is lymphoid leukemia in association with large tumor masses, i.e., lymphosarcoma, usually in the mediastinum, in children (Cooke). In supravital preparations the cells differ from those of lymphoid leukemia (Wiseman; Isaacs). Leukocytosis with circulation of the lymphosarcoma cell is observed in about one-third of cases of lymphosarcoma (Isaacs). This so-called entity,

tion beyond the proposal of more than fifty terms as synonyms. It is of interest, however, that the long-suspected interrelationship of Hodgkin's disease and other lymphatic tumors has been convincingly demonstrated by a recent study of 700 cases of Hodgkin's disease and 600 other lymphatic tumors (Custer and Bernhard). (See section on malignant lymphoma, p. 818.)

Pathologic Anatomy. The cervical lymph nodes are typically affected in Hodgkin's disease. They are large and firm, and only late in the course of the disease do they become fused with one another. In the early stages the lymph nodes may display no gross changes except enlargement. Initially, there is enlargement of the follicles and the node may be only partially replaced by lymphoblasts and swollen reticulum cells, some of which form Sternberg-

Reed cells. This characteristic cell of Hodgkin's disease is about 30 microns in greatest diameter, has an amphophilic cytoplasm, and presents a folded or lobulated nucleus with one or more distinct, usually acidophilic nucleoli. With further progress of the disease the lymphoid tissue is gradually replaced by granulomatous and fibrous tissue so that eventually the architecture of the node is completely destroyed. Plasma cells and eosinophils are usually present. One of the most characteristic gross features at autopsy is the variable appearance of the different nodes. One group of nodes will be fibrotic, others will show the earliest stage, and still others some intermediate stage.

Only about one-fifth of cases of Hodgkin's present a "pure" tumor type. Complete alteration of histologic pattern during the interval between biopsy and autopsy may be expected in about 40 per cent of cases of Hodgkin's disease. Over half of all cases of Hodgkin's disease will also show areas of one or more of the other variants of malignant lymphoma (Custer and Bernhard). Diffuse infiltration or the formation of tumor nodules in the viscera occurs in the late stages. The bones and bone marrow may be affected.

Causal Factors. In most cases of Hodgkin's disease the granulomatous appearance of the lesions is not unlike that of tuberculosis and syphilis. However, no one has successfully identified a causal agent of this disease. Its relationship to other variants of malignant lymphoma is evidence for the neoplastic nature of the group. Nevertheless, there must be recognized the possibility of a virus or other living agent as a factor in etiology of such tumors as malignant lymphoma.

Incidence. Hodgkin's disease shows a preponderance in men of 2 to 1 or 3 to 1. It may begin at any age from infancy to senility, but the highest frequency is between fifteen and thirty-five.

Clinicopathologic Correlation. The signs and symptoms of Hodgkin's disease result from the space-consuming lesion pressing on important structures. From a clinical standpoint the lymph nodes are affected in the following order of frequency: cervical, submaxillary, clavicular, axillary, tracheobronchial, mediastinal, and retroperitoneal. The infiltration and tumors in the spleen and liver bring about conspicuous enlargement of these or-

gans. Careful studies indicate that about 60 per cent of cases start in the peripheral lymph nodes, about 30 per cent in the thoracic lymph nodes, and about 10 per cent in the abdominal lymph nodes and spleen. The cause of the characteristic swinging fever of the Pel-Ebstein type is not clear, but is more common when the abdominal viscera are affected. It is difficult to predict the outcome in any given patient. About 50 per cent die within one year, while isolated reports record survivals of up to twenty years. The diagnosis is almost entirely dependent on a histologic study of an excised lymph node. The only satisfactory treatment is with radiant energy or one of the nitrogen mustard compounds. The anemia is in part a manifestation of emaciation and in part of infiltration and replacement of the bone marrow. The Gordon test depends on the eosinophils in the tissue (Turner, Jackson, and Parker).

Mycosis Fungoides

This entity is not a disease related to a fungus but is a malignant lymphoma. It is a chronic condition in which the conspicuous changes involve the skin. The early lesions are exfoliative, erythematous, eczemoid, urticarial, or of the mixed type. In this so-called pre-mycotic stage the differentiation from the benign inflammatory dermatoses may be difficult. Histologically the pre-mycotic lesion presents a hyperplasia of the epidermis and a dermal perivascular infiltrate of lymphocytes, lymphoblasts, reticulum cells, eosinophils, and sometimes multinucleated cells. Mitoses are numerous, and pyknosis and karyorrhexis of the nuclei of the cells of the infiltrate are frequently found. A characteristic clumping of the nuclei of the infiltrating cells aids in the diagnosis. In the late stage there are nodules or plaques in the skin, sometimes with atrophy and ulceration of the epidermis. The condition may terminate as any one of the varieties of malignant lymphoma.

The skin is involved in some well defined cases of the lymphomas and the leukemias. In the dermis there may be collections of the cells characteristic of the particular disease although in the majority of instances the lesions are either leukemids or are hemorrhages associated with thrombocytopenia (Epstein and MacEachern).

Reticulum Cell Sarcoma

Reticulum cell sarcoma is a variant of malignant lymphoma, closely related to monocytic leukemia and apparently identical with Hodgkin's sarcoma (Custer and Bernhard).

Pathologic Anatomy. The principal gross feature is enlargement of lymph nodes, sometimes in local groups but eventually as a generalized lesion. The capsules may be thickened and the nodes interadherent. The tissue bulges from the cut surface and is grayish white, firm, and finely granular. The spleen is frequently enlarged, and is involved diffusely or by nodules of firm, grayish white, neoplastic tissue. Other tissues may be similarly affected, especially the bone marrow, liver, kidneys, lungs, and other organs where residual lymphoid foci are likely to be present. Primary reticulum cell sarcoma of bone has been reported (Parker and Jackson).

The cells of reticulum cell sarcoma vary within a single patient and from case to case. The architecture of the lymph nodes is effaced by an overgrowth of the neoplastic cells. The most immature cells are 15 to 35 microns in diameter, with abundant pale staining, amphophilic cytoplasm, and a large, vesicular nucleus and a single prominent nucleus. The cells are arranged in solid sheets without clearly discernible cell borders. Similar, better outlined cells have lobulated nuclei and multiple eosinophilic nucleoli to present an appearance indistinguishable from Sternberg-Reed cells of Hodgkin's disease. More mature cells are 14 to 22 microns in diameter with abundant eosinophilic cytoplasm and a round or oval eccentric nucleus without a nucleolus (Warren and Picena). Cases showing immature cells and running an acute clinical course may display foci of necrosis bordered by a zone of reaction suggesting an infectious granuloma. More protracted cases allow time for deposition of reticulin and collagen with scarring in diseased areas.

Clinicopathologic Correlation. The average duration of life after the onset of symptoms is about two years. Occasionally the condition is a localized one, and surgical removal is indicated (Parker and Jackson). The outstanding signs and symptoms result from enlargement of lymph nodes and of spleen. The fever occurring in about a quarter of the cases is possibly associated with necrosis of the neoplastic

tissues. In the late stages the enlarged lymph nodes may press on blood vessels, nerves, and hollow viscera, producing obstruction with secondary changes (Gall and Mallory).

Monocytic Leukemia

Pathologic Anatomy. The gross pathologic changes in monocytic leukemia are not distinctive. The spleen, liver, and lymph nodes are moderately enlarged, gray, and firm, and the architecture is obliterated. The bone marrow may show the usual red and fatty appearance if the duration of the disease is short, or may be gray from massive overgrowth of the leukemic cells in more chronic cases (Fig. 398, *B*). Proliferation of leukemic cells of the monoblastic or monocytic type occurs at sites corresponding to the distribution of the reticulo-endothelial system. Ulceration and inflammation of the gingiva and pharynx and infiltration of the skin are more common in monocytic leukemia than in other varieties of leukemia (Doan and Wiseman; Montgomery and Watkins; Clough; Herbut and Miller).

Incidence. About 13 per cent of all cases of leukemia are of the myelomonocytic (Naegeli) type and about 8 per cent are of the histiomonocytic (Schilling) type. About two-thirds of each of these types are acute and tend to occur in the fourth decade (Bethell).

Relationships and Types of Monocytic Leukemia. The relation of monocytic leukemia to reticulum cell sarcoma has been shown by the demonstration of anatomic changes characteristic of the latter at autopsy of clinical cases of monocytic leukemia (Custer and Bernhard; Doan and Wiseman; Dameshek; Gittins and Hawksley). An intermediate condition, presenting features of both reticulum cell sarcoma and monocytic leukemia, is the so-called reticulo-endotheliosis, most common in children. The liver, spleen, and lymph nodes are involved by monocytic cells and pleomorphic giant cells which also form nodules in the bones and in the skin. In an occasional case 10 to 20 per cent of monocytes are found in the circulating blood (Abt and Denenholz; Sacks). The proliferation of the reticulo-endothelial cells has been frequently observed in monocytic leukemia and there is histologic evidence that the former are precursors of the monocyte (Herbut and Miller). The abnormal reticulum cells observed in monocytic leukemia are sometimes indistinguishable from Sternberg-Reed cells.

Repeated observation of this phenomenon has led to the conclusion that Hodgkin's sarcoma and reticulum cell sarcoma are identical and are very closely allied to monocytic leukemia (Custer and Bernhard). The hemocytologic variations in monocytic leukemia have long been recognized. The Naegeli type presents cells of the myeloblastic type, and all stages between the myeloblast and the adult monocyte may be observed. In the Schilling type only monocytes are found. The larger monographs on this subject (Montgomery and Watkins) should be consulted for detailed discussion of these types.

Clinicopathologic Correlation. The most frequent initial manifestations are pains related to the bones and gingival or nasal hemorrhages associated with thrombopenia. Pathologic fracture may result from the bony changes resembling osteoporosis.

Differential Diagnosis. Required features for the diagnosis of plasma cell leukemia are diffuse involvement of the bone marrow, and plasma cells in the peripheral blood before a terminal stage is reached. Weakness, weight loss, anemia, numbness, and tingling of extremities all may confuse the diagnosis, especially in view of the numerous other diseases

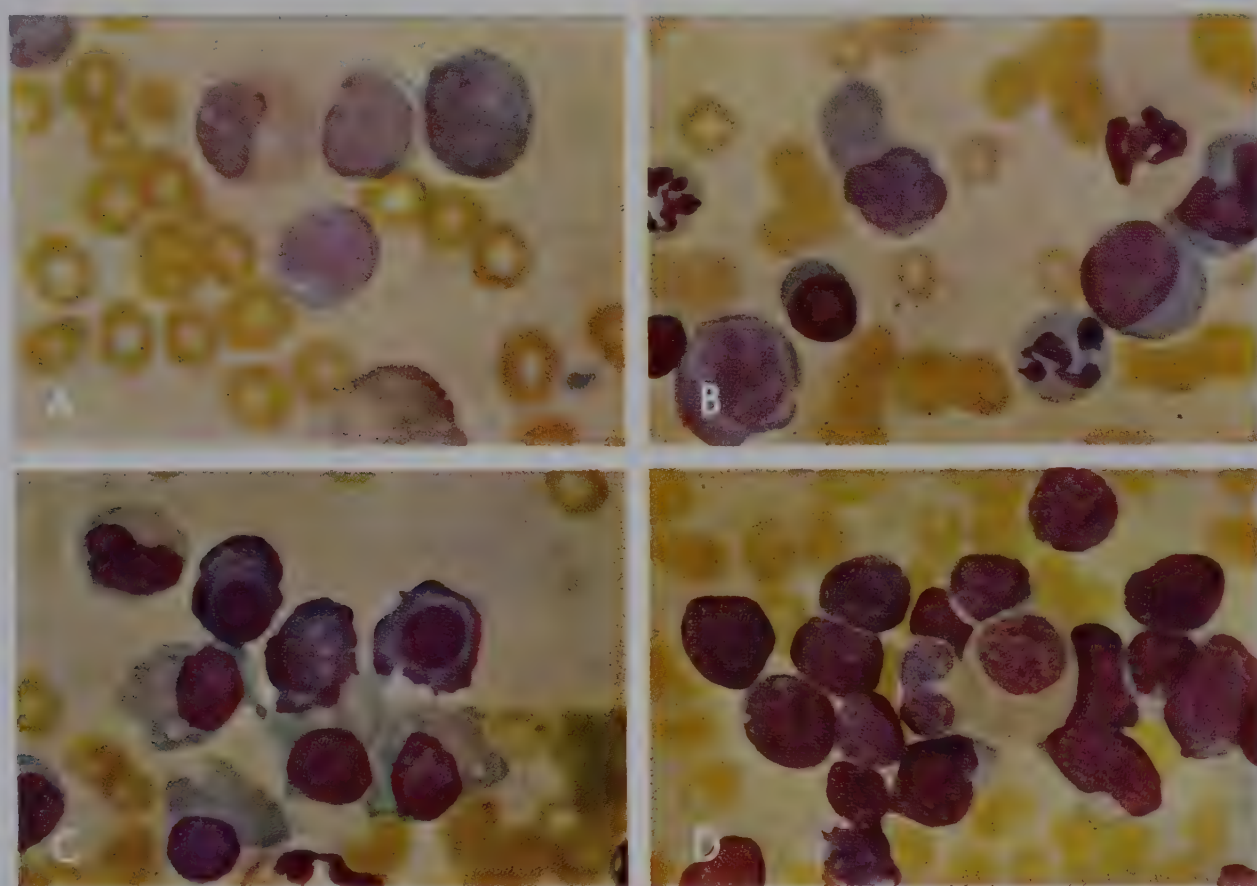


Fig. 398. *A*, Blood in monocytic leukemia. *B*, Bone marrow in monocytic leukemia. *C*, Plasma cells from marrow in a plasma cell myeloma. *D*, Cells in leukosarcoma. (Photographs taken by Dr. Malcolm Cook for Dr. C. V. Moore.)

Plasma Cell Leukemia

Plasma cell leukemia is a rare disease, usually of persons past middle age, occurs with equal frequency in men and women (Moss and Ackerman), and is probably a variant of multiple myeloma. The average length of survival after diagnosis is eight months.

Pathologic Anatomy. There is diffuse involvement of the bone marrow by abnormal plasma cells. The spleen and liver are usually enlarged, the former to 325 or 400 gm. in most cases. The leukemic cells are widely distributed through the tissues generally, and especially in the spleen and lymph nodes.

occasionally associated with circulating plasmacytes. These include measles, myelophthisis of other leukemias or Hodgkin's disease, cirrhosis of the liver, agranulocytosis, gonococcal infection, miliary tuberculosis, infectious mononucleosis, and certain hypoplastic anemias.

Leukemoid Reaction

Under normal conditions the presence within the animal organism of some irritating substance results in a definite and characteristic response of the white blood cells. Under

a variety of poorly understood conditions there may be an abnormal response on the part of the lymph nodes or of the bone marrow, with the pouring into the circulating blood of large numbers of immature cells, with or without an increase in the total white blood cell count. In some of these instances it is extremely difficult to distinguish the hematologic picture from that of leukemia, and the condition has been termed the leukemoid reaction. Either the lymphoid or the myeloid series of cells may be affected (Krumbhaar; Hill and Duncan).

At autopsy there are few gross pathologic changes. The liver, spleen, and lymph nodes are not enlarged as the result of leukemoid reaction, although they may be enlarged because of some associated disease such as infection. The bone marrow is gray or red in color, depending upon the relative amount of hyperplasia of the myeloid or erythropoietic tissue. Since a severe anemia is frequently an associated lesion there may be fatty degeneration of the heart, liver, and kidneys. Microscopically hyperplasia of the myeloid cells of the bone marrow is observed, with retention of some of the more mature cells, thereby differing from true leukemia. Throughout the liver and spleen there are small foci of hematopoiesis, some containing myeloid cells and others containing megaloblasts and normoblasts. Similar changes are found less frequently in the lymph nodes. In all of the smaller blood vessels there may be leukostasis.

Causal Factors. There are two great groups of diseases with which the leukemoid reaction is associated: infections and disseminated malignant neoplasms. The infections appear to be similar to those not associated with the leukemoid reaction, and the neoplasms do not seem to act by metastases to the bone marrow and crowding out of the normal hematopoietic elements (Meyer and Rotter). In many instances the condition is associated with severe hemorrhage and it is possible that this plays some part in initiating the reaction.

Clinicopathologic Correlation. It is impossible to separate the signs and symptoms of the leukemoid reaction from the basic disease. There is no enlargement of the spleen or lymph nodes. The blood count and biopsy of the sternal bone marrow must be depended upon for diagnosis. The total blood count may be elevated or depressed, and the critical change is the presence of immature cells in large num-

bers in the peripheral blood. In a few cases it may be impossible to distinguish the condition from true leukemia (Downey, Major and Noble; Custer).

Infectious Mononucleosis

Pathologic Anatomy. Infectious mononucleosis, or glandular fever, is an acute disease which grossly is almost exclusively confined to enlargement of lymphoid tissues, especially the spleen (Custer and Smith). Nasopharyngeal lymphoid hyperplasia is a constant feature. Other tissues usually present no significant gross features related to the primary disease except for rather consistent enlargement of the liver, infrequent icterus, and occasional cutaneous rash. Microscopic examination reveals widely disseminated perivascular arrangement of normal and abnormal lymphocytes in a manner simulating certain known viral diseases. Reactions of this type may involve any of the tissues except for the bone marrow which in sections is virtually devoid of lymphocytes. In aspirated marrow, lymphocytes occur only because of dilution with peripheral blood and the principal alteration is a myeloid hyperplasia and immaturity (Limarzi, Paul, and Poncher). More specific histologic changes are evident in the lymphoid tissues where the abnormal lymphocyte may be identified in thin, lightly stained sections. Lymph node reactions vary from a predominant follicular hyperplasia to the more commonly encountered blurred pattern (Gall and Stout) simulating malignant lymphoma. The blurred pattern follows lymphocytic and reticulo-endothelial proliferation in the medullary cords. The spleen shows lymphocytes in the thinned capsule and trabeculae. The follicles are widely spaced and the intervening pattern is partially effaced. Normal and abnormal lymphocytes may be identified in the blood sinuses. Accumulations of these are present beneath the intima of intratrabecular veins and constantly separate each intratrabecular artery from its sheath of trabecular substance. Tonsils display exuberant lymphocytic proliferation and may include areas of necrosis. Periportal lymphoid aggregates are common and may be sufficiently advanced to simulate leukemia. Central nervous system involvement is not rare and may produce the Guillain-Barré syndrome (Ricker, Blumberg, Peters, and

Widerman). Pneumonic exudate and interstitial reaction is occasionally lymphocytic.

Incidence. Infectious mononucleosis occurs usually in healthy young adults, throughout the world. Epidemics are most frequent in spring and fall, but sporadic cases occur throughout the year. Both are rare in summer.

Serologic Aspects. A diagnostic feature of infectious mononucleosis is the presence of sheep cell agglutinins (heterophile antibody) in high titer in the blood serum at some time during the course of the disease. Normally, human blood serum in a dilution of 1:8 may cause agglutination of sheep cells, and titers up to 1:56 have been observed in infectious hepatitis (Berk, Shay, Ritter, and Siplet). However, significant increases in heterophile antibody titer occur rarely in infectious hepatitis and, further, the agglutinin in the serum of cases of infectious hepatitis differs from that in infectious mononucleosis in its absorbability by guinea pig kidney. The serum of patients with infectious mononucleosis not infrequently gives a false positive Wassermann test and a false positive agglutination for some of the intestinal pathogens.

Causal Factors. Both the clinical and pathologic features suggest an infectious agent, perhaps a virus, but no agent has been satisfactorily demonstrated.

Clinicopathologic Correlation. The most frequent complaints in infectious mononucleosis are sore throat, enlarged lymph nodes, and fever (Read and Helwig); these and other less frequent findings are a part of the lymphoid response to the causative agent which is probably an infective one. The enlargement and lymphocytic involvement of the liver is evidence to explain the jaundice and the frequent abnormal results of liver function tests (DeMarsh and Alt; Berk, Shay, Ritter, and Siplet). Bleeding from the gums and nose, observed in 1 or 2 per cent of cases, probably is part of the thrombocytopenic variant of the disease. Rupture of the spleen is a complication accounting for a considerable proportion of the deaths. The cellular reaction, thinning and dilution of the taut splenic capsule, and trabeculae make one wonder that the spleen ruptures so infrequently (Smith and Custer). The respiratory paralysis in Guillain-Barré syndrome associated with infectious mononucleosis accounted for 6 deaths in one epidemic of 500 cases (Thomsen and Vimtrup). The

neuronitis and encephalitis simulate certain viral diseases in extent and cellular reaction.

Infectious Lymphocytosis

Pathologic Anatomy. The principal lesions of the disease are probably limited to the lymphoid tissues although the lymph nodes and spleen are not enlarged clinically. Microscopically, the nodes display marked proliferation of the reticulo-endothelium of the sinuses, which are almost completely blocked by masses of these cells (Foot, quoted by Smith). Occasional large, atypical cells occur in the follicles which are obliterated to a variable degree, in some instances show no germinal centers, and in others exhibit hyaline degeneration. Eosinophils may be present. The bone marrow shows no alteration except for the increased lymphocytes in the blood vessels.

Incidence. The disease is mainly one of young children and is regarded as both infectious and contagious (Smith). The incubation period is possibly twelve to twenty-one days.

Clinicopathologic Correlation. The most characteristic feature is a hyperleukocytosis with relative and absolute lymphocytosis persisting for a long period. The lymphocytes are small and morphologically normal. Signs and symptoms may be virtually absent or may be in the form of an upper respiratory infection, vomiting, irritability, and fever, together with acute abdominal findings and occasional signs of involvement of the nervous system. Enlargement of lymph nodes and spleen is usually absent. The clinical manifestations may possibly be explained by lymphocytic reaction in the systems involved clinically, although no autopsies have been reported in this relatively benign disease. The heterophile agglutination reaction is uniformly negative. It is important to differentiate this disease from leukemia of children in which the cells are virtually always immature and the spleen enlarged (Moyer and Fisher).

Hypersplenism

Those conditions showing increased destruction of blood cells, compensatory hyperplasia of the bone marrow, and cure by splenectomy fulfill the criteria necessary for the diagnosis of hypersplenism. These conditions are: splenic neutropenia, splenic anemia (familial

or acquired hemolytic icterus), splenic thrombopenia (idiopathic thrombocytopenic purpura), and splenic panhematopenia, depending on the cell or cells affected by the spleen.

Pathologic Anatomy. The spleen is usually enlarged, but not necessarily so, in the hypersplenic states. In general, the histologic picture is not diagnostic but consists principally of hyperplasia of the reticulo-endothelial cells, not including the cells of the inconspicuous germinal centers. Phagocytosis of the blood cells is difficult to demonstrate in the usual tissue sections but by supravital technique there may be found cells or fragments of cells within phagocytes (Moore and Bierbaum).

Mechanism of Cell Destruction. Doan cites evidence suggesting that there are abnormal stasis in the splenic pulp and/or sinuses calling for compensatory increase in delivery of marrow elements; deplasmation with increased mechanical intercellular friction; pathologic concentration of lysolecithin and other substances produced by the reticulo-endothelial cells and tending to destroy blood cells; exceptional opportunity for contact phagocytosis by the reticulo-endothelial elements. Indirect evidence of the abnormal stasis may be demonstrated by careful studies of peripheral blood cells and blood volume before and after the injection of epinephrine, the drug causing

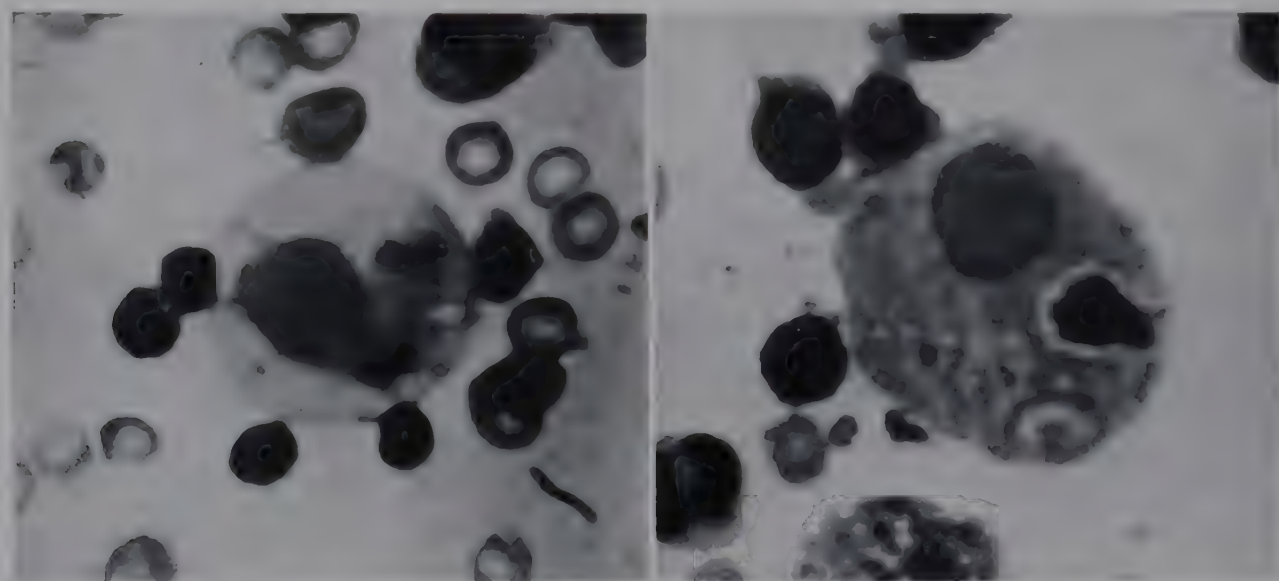


Fig. 399. Phagocytosis of leukocytes in the spleen in chronic splenic neutropenia. (Case reported by Moore, C. V., and Bierbaum, O. S.: *Internat. Clinics*, Vol. 3, 1939.)

Characteristic especially of splenic anemia is the engorgement of the red pulp by erythrocytes and the empty state of the sinusoids (Doan; Von Haam and Awny). The fragile spherocytes, commonly found in the familial variety of splenic anemia, are usually not identifiable in tissue sections.

Compensatory changes in the bone marrow are represented by the myeloid hyperplasia in splenic neutropenia, the erythroid hyperplasia in splenic anemia, and the megakaryocytic hyperplasia with a diminished formation of platelets in splenic thrombopenia (idiopathic thrombocytopenic purpura). A diffuse, non-specific type of hyperplasia occurs in splenic panhematopenia. About one-third of cases of hypersplenism are secondary to some disease showing cellular proliferation with increase in size and activity of the spleen. These include congestive states, infiltration by lipids, chronic granulomatous inflammation, leukemias, and other tumors (Doan).

splenic contraction and a release of the entrapped cells into the circulation.

Neutropenia

By the term "neutropenia" is meant a distinct disease, one sign of which is a relative decrease in the number of polymorphonuclear leukocytes in the circulating blood. This is in contrast with leukopenia, which is a nonspecific sign of many pathologic processes.

Neutropenia may exist as a chronic, asymptomatic process which is discovered only during the course of a routine blood count, but it is usually recognized as acute neutropenia or agranulocytosis. This latter term is undesirable, since there is ordinarily not complete absence of leukocytes.

Pathologic Anatomy. At autopsy the principal pathologic changes are found in the bone marrow and in the pharynx. The picture in the bone marrow depends on the chronicity of the

condition. In those who die within a few days there is hyperplasia of the bone marrow, with large numbers of immature myeloblasts (stem cells). These cells are large, 15 to 25 microns in diameter, round or polygonal, with a palely basophilic cytoplasm and a large reticulated nucleus with a prominent nucleolus. Mitotic figures are moderately abundant. In the person who survives for several weeks, the normal myeloid elements of the bone marrow practically disappear, and the marrow is composed almost entirely of the erythropoietic tissue and infiltrated lymphocytes and plasma cells. If the bone marrow is studied during the period of improvement in a patient who eventually recovers, there is found a progressive increase in the number of myelocytes and young polymorphonuclear leukocytes (Darling, Parker, and Jackson). In the pharynx there is an acute necrotizing inflammation, dark purple in color, which microscopically shows necrosis of tissue, exudation of fluid and fibrin, but with only an occasional wandering cell, almost always a lymphocyte or a mononuclear cell. There is not infrequently an associated bronchopneumonia, which shows the same characteristics: an inflammation with fluid and fibrin, but without cells.

Causal Factors. Chronic neutropenia is not well understood, and may represent a constitutional defect in the lability of the bone marrow. Acute neutropenia is well understood, and may result from any of a variety of bacterial, chemical, or physical agents, the most important of which are the drugs, amidopyrine and the sulfonamide derivatives. Less important are dinitrophenol and arspenamine (Kracke). The fact that all of these drugs do not regularly produce the disease has led many to suppose that idiosyncrasy or sensitization is also a factor.

Histologic studies show an apparent hyperplasia of stem cells in the bone marrow, indicating that the basic defect in this disease is a lack of maturation of the cells of the myeloid series (Fitz-Hugh and Krumbhaar). This is further supported by the studies indicating that a poorly defined nutritional factor may be responsible for a rare case of neutropenia (Miller and Rhoads).

Clinicopathologic Correlation. The signs and symptoms of acute neutropenia are largely those of infection of the upper and lower respiratory tract: generalized pains, chills, fever,

headache, and nausea. The edema in the mucosa of the respiratory tract may lead to dyspnea and even cyanosis. The mortality ranges from 70 per cent to 90 per cent. The condition is to be distinguished from a leukopenia caused by some specific infectious disease such as influenza, from aleukemic leukemia, from infectious mononucleosis, and from aplastic anemia (Reznikoff).

Tumors of the Spleen

Primary neoplasms of the spleen are rare. Small hemangiomas and lymphangiomas are occasionally seen as incidental findings. Rarely these reach large size and produce symptoms. Sarcoma is the commonest of splenic neoplasms and may be a spindle-cell or round-cell sarcoma. Metastases to the spleen occur in about 2 to 3 per cent of all malignant tumors, especially from those of the stomach, pancreas, and breast (Krumbhaar).

Hemangioma of the Spleen. Hemangioma is the most frequent benign neoplasm of the spleen. It occurs as a moderately well demarcated, dark red, trabeculated nodule, usually just beneath the capsule. They are frequently multiple. Occasionally the tumor reaches large size, with clinically demonstrable enlargement of the spleen, requiring surgical intervention. Large vascular spaces separated from one another by delicate connective tissue trabeculae and lined by endothelium are seen microscopically. Secondary changes, as thrombosis, fibrosis, and calcification, are common (Pines and Rabinovitch).

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THE ENDOCRINE GLANDS

XCV

General Considerations. Diseases of the Thyroid Gland

The endocrines or ductless glands elaborate hormones (from the Greek word “to excite”). A hormone may be defined as a chemical substance which is formed in one part of the body and is carried in the blood to another organ

still others are relatively simple cyclic compounds: epinephrine from the adrenal medulla, and thyroxine from the thyroid.
Types of Study. Excess and Deficiency.
The effect of the secretion of an endocrine

TABLE 47. EFFECTS IN MAN OF DEFICIENT OR EXCESSIVE SECRETION OF ENDOCRINE GLANDS

Gland	Deficiency	Excess
Anterior lobe of pituitary:		
All hormones:		
Prepuberal.....	Nanosomia	
Postpuberal.....	Simmonds' disease	
Hormones of acidophilic cells:.....		
Prepuberal.....	Gigantism
Postpuberal.....	Acromegaly
Gonadotropic hormones (pituitary or placental).....	Chorio-epithelioma and some teratomas
Posterior lobe of pituitary and hypothalamus.....	Diabetes insipidus or adiposogenital dystrophy or combinations	
Thyroid.....	Myxedema Cretinism	Hyperthyroidism
Adrenal cortex:		
Interrenal.....	Addison's disease	
Androgenic.....	Androgenital syndrome
Adrenal medulla.....	Pheochromocytoma (paroxysmal hypertension)
Parathyroid.....	Tetany	Hyperparathyroidism
Testis.....	Eunuchism Eunuchoidism	Interstitial cell tumor
Ovary.....	Eunuchism Eunuchoidism	Functional tumors of theca, granulosa, or lutein cells

or tissue and influences its activity (Best and Taylor). In most instances the hormones have been isolated in a relatively pure state, or have been crystallized. Some are steroids: testosterone from the testis, and corticosterone from the adrenal cortex; others are proteins: parathormone from the parathyroid, and the complex target hormones from the pituitary; and

gland may be studied in the deficiency states resulting from surgical removal or destruction by disease, and in those states in which excessive amounts are either introduced by parental injection or elaborated by a diseased gland. In animals, the problem is relatively simple, but in man much more information is needed to complete the picture. Table 47 will

give some idea of the possible combinations.

Each of the conditions listed in Table 47 is discussed in succeeding pages, but there are other equally definite conditions considered which do not fit into the table. This probably means that our knowledge of them is not complete. There is also the possibility of perverted secretion in addition to simple deficiency and excess of the normal substances.

Interrelations of the Endocrine Glands. The products of the endocrine glands affect not only tissues in general, but also the other endocrine glands. To cite a few examples: cysts of the ovaries with excessive chorionic gonado-

larger the so-called "normal thyroid" in any given location, the higher the frequency of goiter (any enlargement of the thyroid). This difference is apparent at birth and continues throughout life, as shown in the figures collected by Wegelin (Table 48).

Classification of Diseases. Our knowledge at the present time is not adequate to present a unified picture with clinicopathologic correlation. Although at times a certain histologic structure appears to accompany a definite functional state of hypothyroidism or hyperthyroidism, it is not consistent. Hence it seems best to present the various anatomic

TABLE 48. GEOGRAPHICAL VARIATIONS IN WEIGHT OF THYROID

Age	Kiel, Germany: Nongoitrous District (Thyroid Weight in Gm.)	Bern, Switzerland: Goitrous District (Thyroid Weight in Gm.)
Newborn to 10 days.....	1.90	8.20
6 months.....	1.55	2.90
1 year.....	2.40	5.33
6 to 10 years.....	7.40	18.58
21 to 30 years.....	23.50	43.00
51 to 60 years.....	19.00	47.00

trophin in hydatidiform mole; enlargement of the thyroid, parathyroids, and adrenals in acromegaly; and enlargement of the pituitary after castration. The intimate interrelation is well shown in the Houssay experiment: removal of the pancreas results in diabetes, but if the pituitary is then removed the diabetes is no longer evident. I have seen a similar situation in which a child with tetany was cured of tetany when the adrenal insufficiency of Addison's disease supervened. Because of these interrelations, it is possible for a lesion of any of several different organs to give the same result: the syndrome of Cushing (basophilism) is associated with a lesion of the hypothalamus, an adenoma of the adrenal cortex, or a thymoma.

General Considerations of the Thyroid Gland. Classification of Diseases

The secretion of the thyroid gland is necessary for normal growth and development, and for maintenance of normal metabolism (Lerman).

Geographic Location and Size. The normal size and weight of the thyroid gland vary in different parts of the world. In general, the

entities and then the clinical conditions. The approach is essentially that of Wegelin.

Anatomic Classification:

- 1. Congenital anomalies
- 2. Diffuse hyperplasia
- 3. Nodular hyperplasia
- 4. Adenoma
- 5. Malignant adenoma
- 6. Carcinoma
- 7. Struma lymphomatosa
- 8. Riedel's struma

Clinical Classification:

- 1. Athyroidism and hypothyroidism
 - (a) Endemic cretinism
 - (b) Myxedema and sporadic cretinism
- 2. Hyperthyroidism
 - (a) Endemic goiter (discussed on p. 64)
 - (b) Basedow's disease
 - (c) Toxic nodular goiter

Congenital Anomalies of the Thyroid

The thyroid gland is formed as a diverticulum of the floor of the pharynx at a point on the base of the tongue, to be recognized in adult life as a dimple—foramen caecum. The distal end of the diverticulum enlarges to a solid mass of cells connected to the tongue by a narrow stalk—the thyroglossal duct. With shifts in the relative positions of structures in

the neck, the thyroid comes to lie over the thyroid cartilage of the larynx.

The simplest logical anomaly is a failure of migration and shift, so that the thyroid remains as a projecting mass on the base of the tongue—lingual thyroid (full discussion, p. 639). If shift does occur, the thyroglossal duct may persist as a continuous fistulous tract, or as discontinuous cysts, filled with a clear fluid and lined by ciliated columnar or stratified epithelium. Beneath the epithelium is a tissue rich in lymphoid cells, indicative of a

normal, although each lobule is larger. The color and translucency vary with the amount of colloid, from the brown translucence of conspicuous colloid to the yellow-gray opacity of scant colloid. Two types are recognized: congenital hyperplasia and hyperplasia of children and adults.

Congenital Hyperplasia. In goitrous regions the thyroid gland in as many as 80 per cent of all newborn children may exceed the maximum normal weight of 3 gm. The thyroid may consist of numerous solid or acinic glands

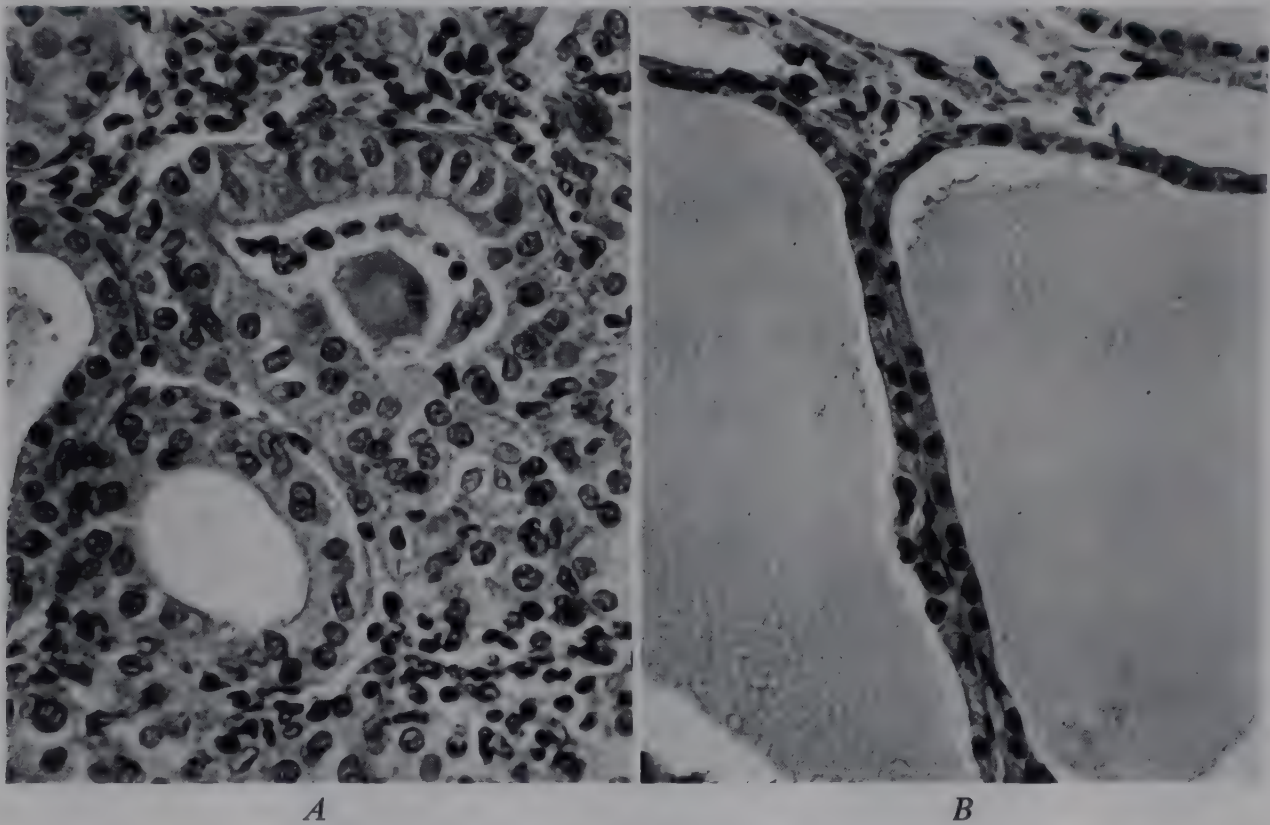


Fig. 400. The two phases of hyperplasia of the thyroid. *A*, Tall columnar cells with little colloid of active hyperplasia. *B*, Cuboidal cells with stored colloid of involution. (Armed Forces Institute of Pathology, Neg. Nos. 75824 and 75825.)

relation to the pharyngeal mucosa. In the surrounding fibrous tissue are small typical or atypical thyroidal acini. A long fistulous tract may penetrate through the hyoid bone. Secondary infection is not infrequent.

Agenesis, aplasia, and hypoplasia have been observed. Accessory masses of thyroidal tissue may be present at the base of the tongue, along the midline of the neck, in the anterior mediastinum, laterally as far as the axilla, and behind or in front of the normal gland. The so-called “lateral aberrant thyroid” is considered elsewhere (p. 641).

Diffuse Hyperplasia of the Thyroid

The thyroid gland in diffuse hyperplasia is enlarged uniformly. The lobular structure is

composed of columnar or cuboidal cells without demonstrable colloid, of similar structure except that there are prominent vessels, or of conspicuous colloid storage in acini lined by cuboidal or cylindrical cells.

The congenital goiter contains little or no iodine, and is ineffective in bringing about metamorphosis in tadpoles. It is possible that congenital goiter is a response of the fetus to hypothyroidism in the mother.

Hyperplasia in Children and Adults. On the basis of the size of the follicles, a microfollicular and a macrofollicular or colloid type may be distinguished.

Microfollicular Form. This is characterized by large lobules composed of small, empty acini, lined by cuboidal or cylindrical epithelium, with large atypical nuclei. Papil-

lary projections into the large acini are present. The intralobular stroma is scant.

Colloid Form (Diffuse Colloid Goiter). This is an important type in regions where goiter is endemic. It is seen in young adults, and is equally frequent in both sexes. The gland rarely exceeds 70 gm. in weight. It is firm and brownish yellow. The septa are thin. The acini average from 150 to 300 microns in diameter. The epithelium varies from a low cuboidal to a high columnar. The columnar cells are collected in small foci which project into the lumen. The colloid is moderately

as "nodular hyperplasia," "adenomatoid goiter," "adenomatous hyperplasia," and "nodular goiter."

Pathologic Anatomy. Throughout the gland are nodules, 0.5 to several cm. in diameter, composed of translucent, firm, brownish tissue. The nodule is not sharply circumscribed, and is not encapsulated. The surrounding tissue is frequently compressed. Within the nodule the acini average 300 to 500 microns in diameter, but a rare one may measure 1 mm. The epithelium is cuboidal or flattened, with occasional islands of columnar cells. Spurs of

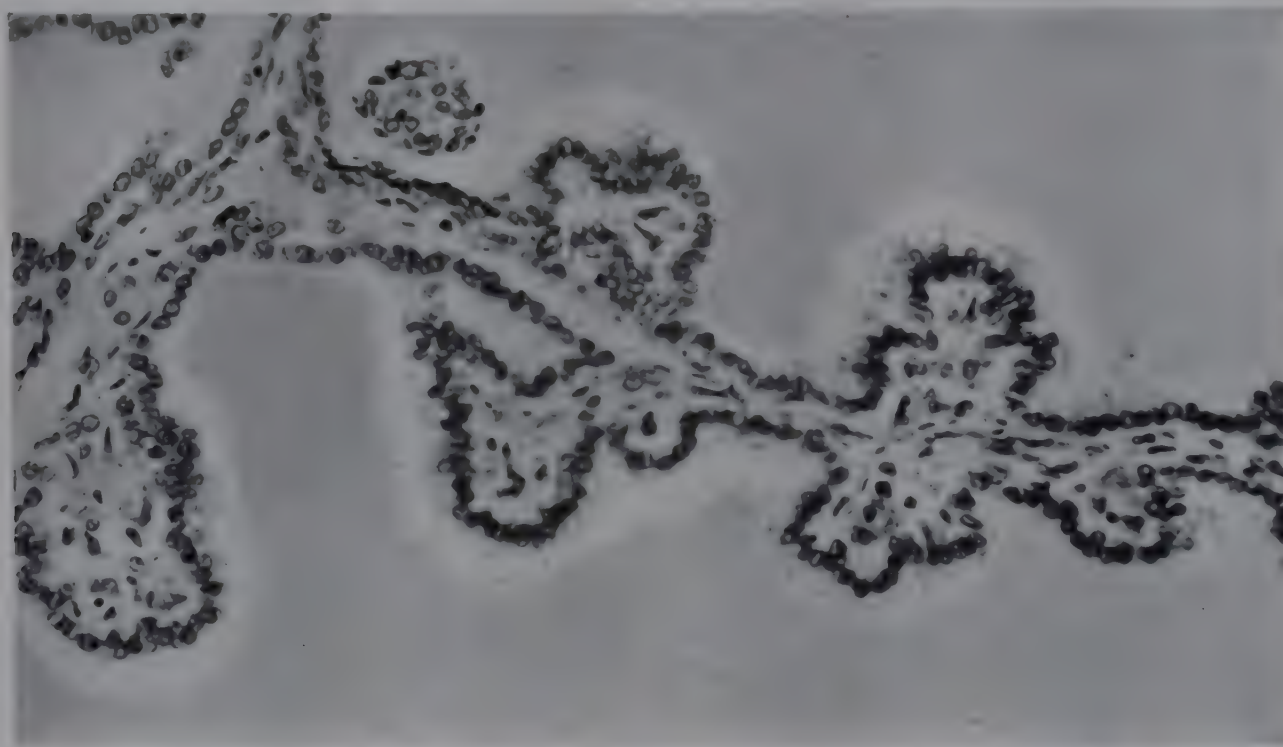


Fig. 401. Active secretion of colloid. Note tall cells, papillae, and vacuoles. (Armed Forces Institute of Pathology, Neg. No. 75852.)

dense, and shows little or no vacuolation, either in the center, or at the edge as scalloping. The content of iodine is increased over the normal.

Transition Forms. Transition forms between the microfollicular and macrofollicular forms are observed, and it seems there is a constant movement from hyperplasia to colloid storage and back again. Further evidence for this view is given in the occurrence of slight hyperplasia during each menstrual cycle, during pregnancy, and during and after an infectious disease.

Nodular Hyperplasia of the Thyroid

More than half of all persons over forty living in a goitrous district have enlarged, nodular thyroid glands, variously designated

acinic walls project into the larger cavities, and this suggests that they represent a confluence of smaller acini.

Secondary Changes. Degenerative changes are commonly observed. The septa between the acini undergo hyalinization, and a large focus may become liquefied and appear as a cyst. Hemorrhage into the septa and into the colloid is seen as extravasated red cells or as hemosiderin in macrophages. Calcification in regions of necrosis and hemorrhage is an almost constant lesion.

Pathogenesis. The thyroid over a period of years is subjected to repeated stimuli to hyperplasia, each lasting for a few days or weeks. The stimulus may be the fever and toxemia of an infectious disease, the recurring menstrual cycle, a pregnancy, or an emotional upset. After each stimulus is withdrawn, there

is involution and colloid storage. That during this cycle there are small foci in which the cells undergo greater hyperplasia and involute to a minimal extent is the theory proposed to explain nodular hyperplasia (Rienhoff; Kline). This theory would explain the gradual increase in nodules after the age of fifteen or twenty, and the somewhat higher incidence in women.

ular hyperplasia" and in another as "adenoma."

Adenoma of the Thyroid

The criteria for the diagnosis of adenoma of the thyroid are: complete encapsulation, with the capsule distinct from surrounding compressed thyroidal stroma; uniform inter-

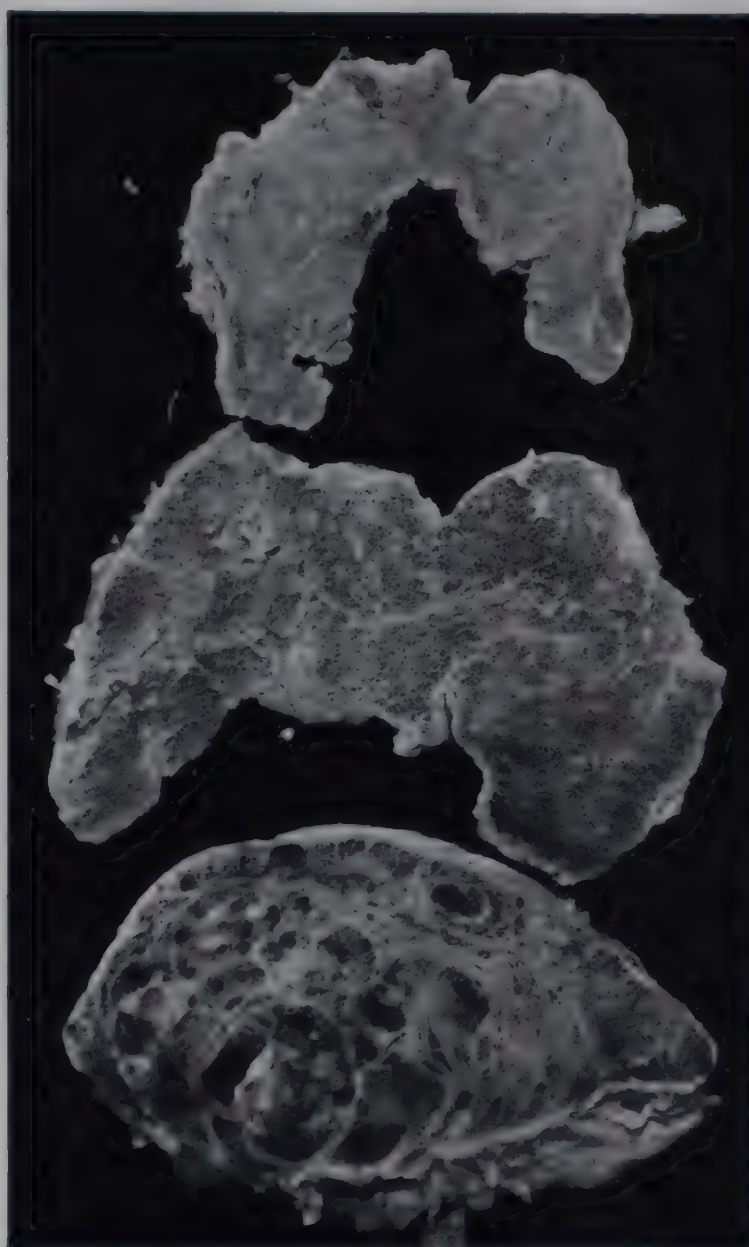


Fig. 402. Three distinctive types of disease of the thyroid. *Above*, Hyperplasia. *Middle*, Colloid storage. *Below*, Nodular hyperplasia. Compare size and structure of cut surface.

Relation to Adenoma. It is not always possible to differentiate nodular hyperplasia from adenoma. Some investigators differentiate largely on size (adenomas are larger), or on the presence of a definite capsule (adenomas have a capsule), or on the response of the cells to the usual stimuli of hyperplasia and involution (adenomas are neoplastic and autonomous). It is clear that modern criteria are not adequate, and identical lesions will continue to be known in one laboratory as "nod-

nal structure, except for foci of secondary change; a difference in the structure of the nodule and that of the remainder of the thyroid; and evidence of compression of the thyroid by the nodule (Lahey, Hare, and Warren).

Types. On the basis of microscopic structure of the adenoma, many different classifications have been proposed. The most satisfactory is one with the following types: embryonal (trabecular), fetal (tubular), mi-

crofollicular, macrofollicular (colloid), papillary, and Hürthle cell.

The *embryonal* and *fetal* types are so named because of their resemblance to the corresponding stage in the genesis of the thyroid. In the former there are solid columns of polyhedral basophilic cells in an edematous stroma. In the latter there are columns with a central lumen filled with a thin colloid and lined by cuboidal basophilic cells. The stroma is distinctive and resembles colloid in that it is relatively avascular and free of stromal

roid may be single or multiple, and may vary in size from less than a millimeter to 10 cm. They rarely exceed 150 gm. in weight. The tissue is soft and grayish red, and bulges from the cut surface. There is a sharp and definite capsule. Throughout the nodule, especially in the larger tumors, there are extensive secondary changes: fibrosis and hyalinization of the stroma, mucoid degeneration of the stroma, fatty degeneration of the epithelial cells, cystic transformation of a small or large focus, either by follicular dilatation or by ne-

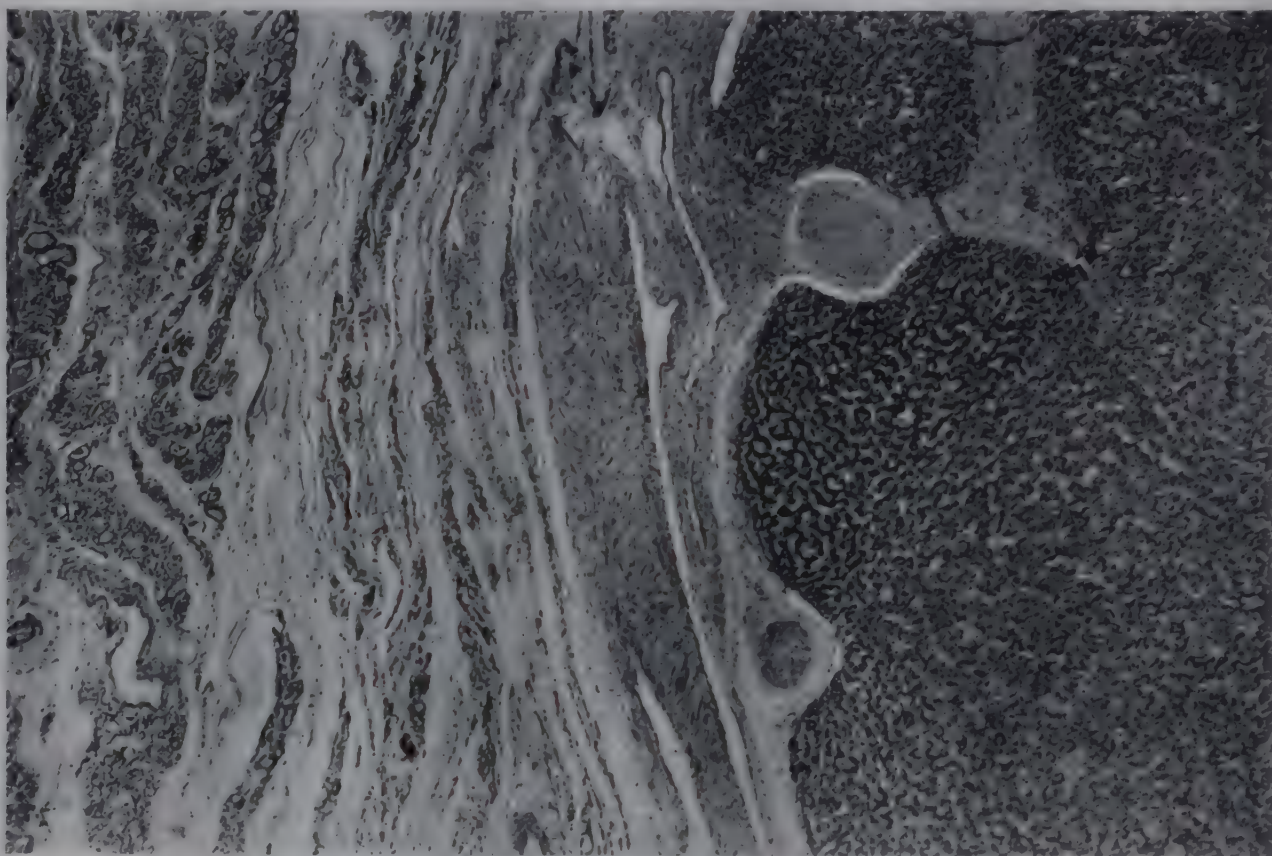


Fig. 403. Edge of fetal adenoma of thyroid. (Armed Forces Institute of Pathology, Neg. No. 75828.)

cells. This has led some to postulate that the fetal adenoma is in fact a growth of small acini into preexisting colloid (Murphy and Ahnquist).

The *microfollicular* (simple) and *macrofollicular* (colloidal) differ only in the size of the follicles. In the first the acini are within the normal range of size, while in the second there are many large follicles up to several millimeters in diameter. In both, the lining cells vary from cuboidal to columnar.

The *papillary cystadenoma* consists of irregular papillary projections of delicate connective tissue, covered by a single layer of all columnar cells. The *Hürthle cell* variety is rare, and the cellular type is similar to that of the corresponding carcinoma (p. 840).

Pathologic Anatomy. Adenomas of the thy-

roid may be single or multiple, and may vary in size from less than a millimeter to 10 cm. They rarely exceed 150 gm. in weight. The tissue is soft and grayish red, and bulges from the cut surface. There is a sharp and definite capsule. Throughout the nodule, especially in the larger tumors, there are extensive secondary changes: fibrosis and hyalinization of the stroma, mucoid degeneration of the stroma, fatty degeneration of the epithelial cells, cystic transformation of a small or large focus, either by follicular dilatation or by ne-

Chemical Aspects. The amount of iodine in the tissue of an adenoma varies directly with the degree of differentiation: little or none in the embryonal and fetal types, and up to the normal in the macrofollicular. The histologic structure, however, is not always correlated with the content of hormone as tested biologically. Ingestion of iodine has in general little effect on the appearance of the undifferentiated adenoma; in other words, the cells are autonomous and do not react to the usual stimulus of involution. The microfollicular and macrofollicular adenomas may respond to iodine as a hyperplastic thyroid does.

Malignant Adenoma

During the first forty years of the clinico-pathologic study of the thyroid, investigators were confronted by a paradox—nodules of what appeared histologically to be normal thyroid tissue in many parts of the body, and only an adenoma in the thyroid itself. The contradictory terms “benign metastasizing thyroid” and “metastasizing struma” were applied to the condition.

Pathologic Anatomy. The excellent studies of Graham resolved the paradox and fur-

appears roughened or the lumen is filled with a thrombus or tissue (Warren).

Malignant Adenoma (Proliferating Struma) of Langhans. This is a special type of multiple lobulated malignant adenoma. It is composed of more or less solid epithelial islands, 100 to 500 microns in diameter, separated by thin trabeculae. The cells are polygonal, with large dense nuclei.

Metastases. The usual malignant adenoma and the Langhans type metastasize by the blood stream, and secondary deposits may be present in any organ or tissue, but most com-

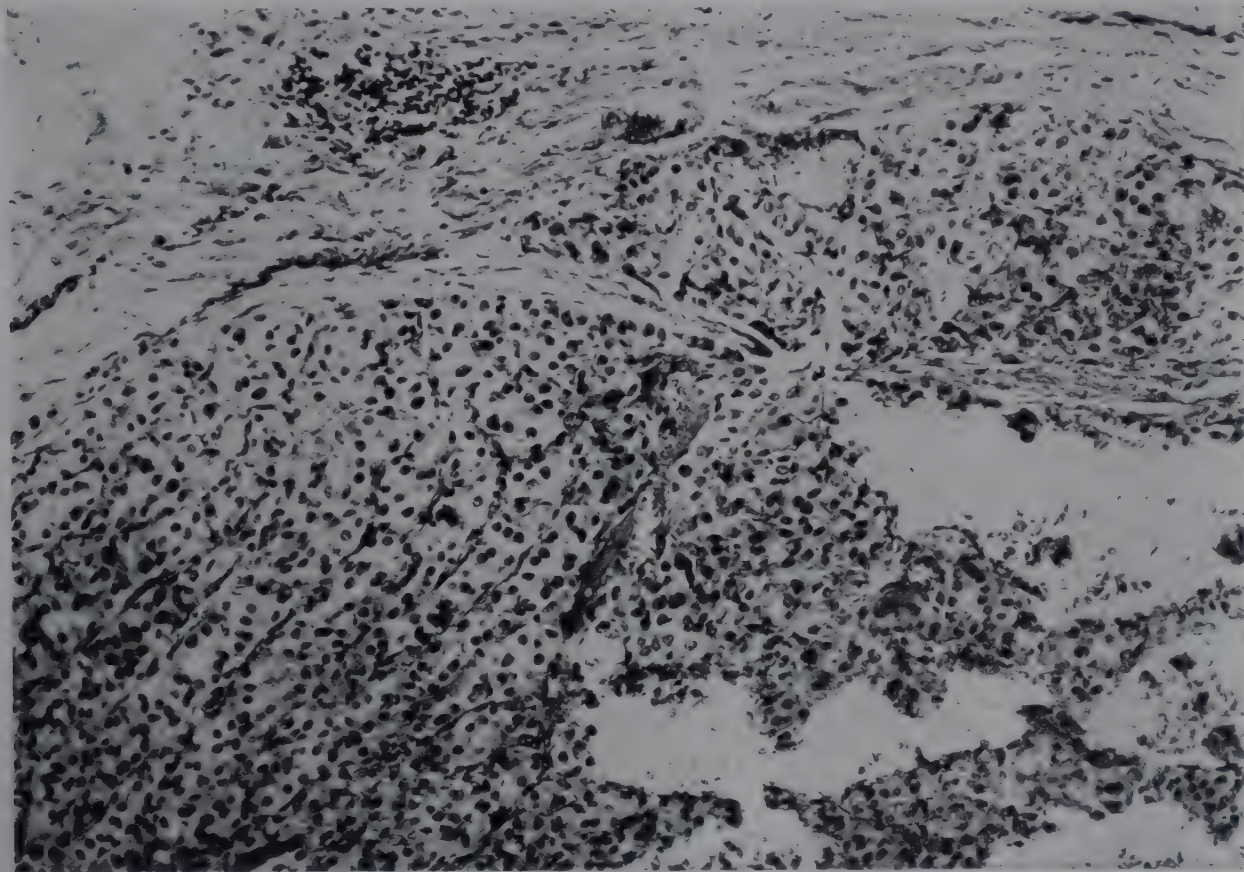


Fig. 404. Invasion of blood vessel by malignant adenoma of thyroid. (Slide by courtesy of Dr. Nathan Womack.)

nished an explanation for the metastases. In the capsule of adenomas of this sort, invasion of blood vessels is readily seen grossly and microscopically. Otherwise there is no essential difference in the adenoma and malignant adenoma. The latter may be any one of the types described in the preceding section. The papillary cystadenoma is to be considered malignant if there is invasion of the capsule, as well as when the veins are eroded.

No pathologic examination of an adenoma of the thyroid is complete until the vessels, usually prominent and numerous, in the capsule have been opened longitudinally or sagittally, and blocks for microscopic study taken from all regions in which the endothelium

monly the lungs and bones. The malignant papillary cystadenoma metastasizes also by the lymphatics, and the regional nodes may be enlarged. It has been postulated by some that most of the papillary cystadenomas of the lateral aberrant thyroid are in fact nodal metastases of a primary neoplasm in the thyroid. Distant metastases occur late, but local recurrence after attempted removal is a common observation.

Carcinoma of the Thyroid

It is useful in an evaluation of prognosis to divide carcinomas of the thyroid into two groups: (1) the adenocarcinomas with a moderate grade of malignancy, and (2) a heter-

ogeneous group (small cell, giant cell, and epidermoid cell carcinoma) with a high grade of malignancy (Lahey, Hare, and Warren; Warren).

Pathologic Anatomy. All types have the same general macroscopic appearance. The

trachea. Metastases to the regional nodes, and systemic metastases, especially to the lungs and bones, are observed.

Adenocarcinoma. Three varieties of adenocarcinoma may be differentiated: papillary, alveolar, and Hürthle cell. Papillary adeno-

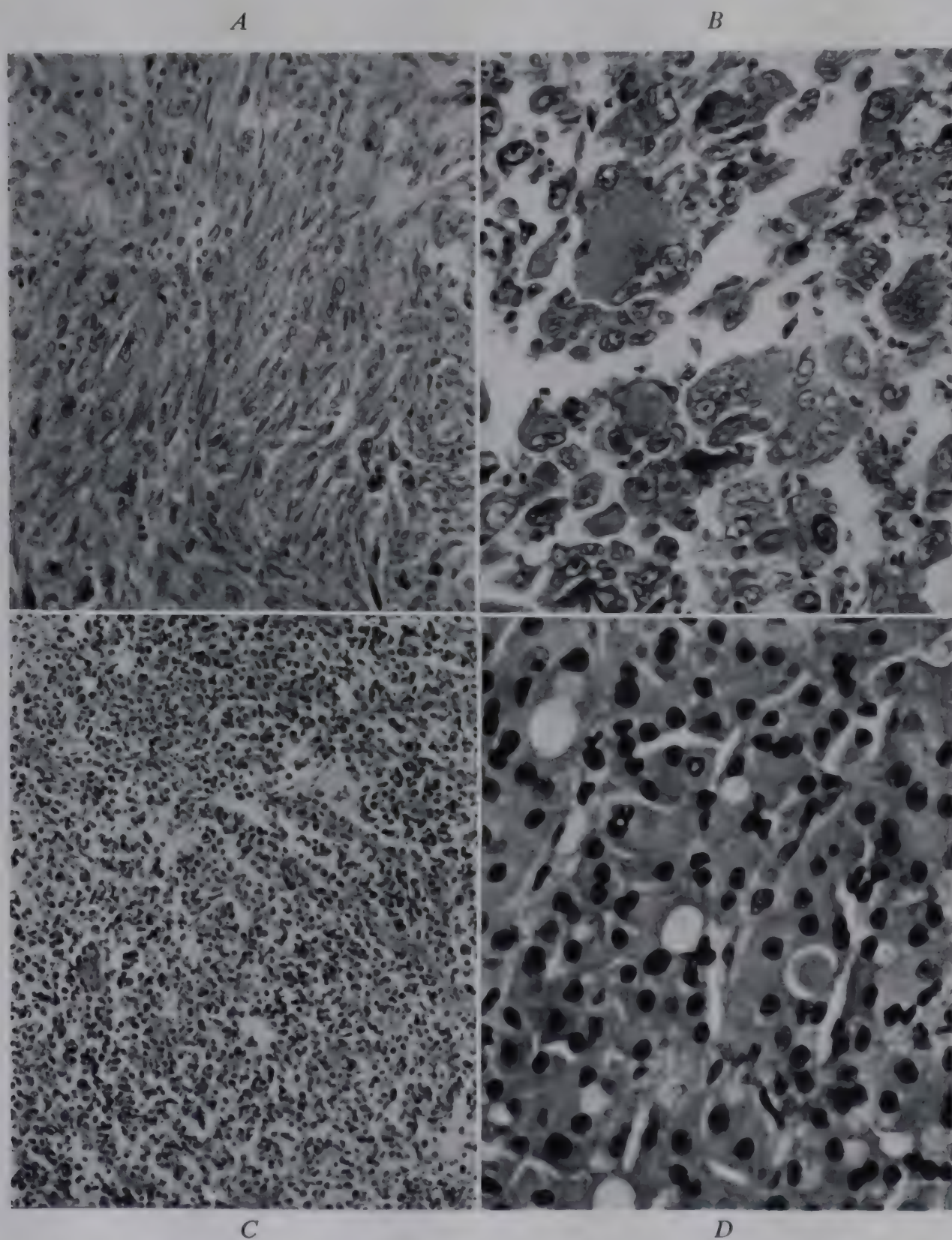


Fig. 405. Carcinoma of thyroid. *A*, Spindle cell carcinoma. *B*, Giant cell carcinoma. *C*, Small cell carcinoma. *D*, Hürthle cell carcinoma. (Armed Forces Institute of Pathology, Neg. Nos. 77420, 77419, 75821, and 77407, from material contributed by Dr. Shields Warren.)

thyroid gland is enlarged and firm. The lobular architecture of brown translucent tissue is lost and replaced by a firm gray or grayish white fibrillar tissue. As the tumor enlarges, the outlines of the gland are lost, and there is fixation to the surrounding skin, muscles, and

carcinoma differs from papillary cystadenoma in showing invasion of the capsule and surrounding thyroid, stratification of cells on the papillae, anaplasia of cells as expressed in variation in size and shape, moderately abundant mitoses, and foci of solid masses of cells.

Alveolar carcinoma varies from a carcinoma simplex to a fully developed adenocarcinoma. The stroma is moderately abundant and dense. The cell of the *Hürthle type* is a large cell with conspicuous cell membrane, prominent, pale, homogeneous or finely granular, acidophilic cytoplasm, and a large vesicular nucleus. The shape is usually tall cuboidal or columnar. The distinction between the Hürthle cell adenoma and carcinoma is based on irregularity in arrangement and loss of definite acinic structure (Wilensky and Kaufman).

spindle-shaped, arranged in bundles (Fig. 405, *B*).

Epidermoid Carcinoma. This rare type has the usual histologic appearance of epidermoid carcinoma. It arises either from the thyroglossal duct or by metaplasia or prosoplasia of thyroïdal epithelium.

Histogenesis. On the basis of chronologic sequence and of histologic appearances it is estimated that 90 per cent of carcinomas of the thyroid originate in an adenoma or in a focus of nodular hyperplasia. The undifferentiated varieties of adenomas—embryonal,

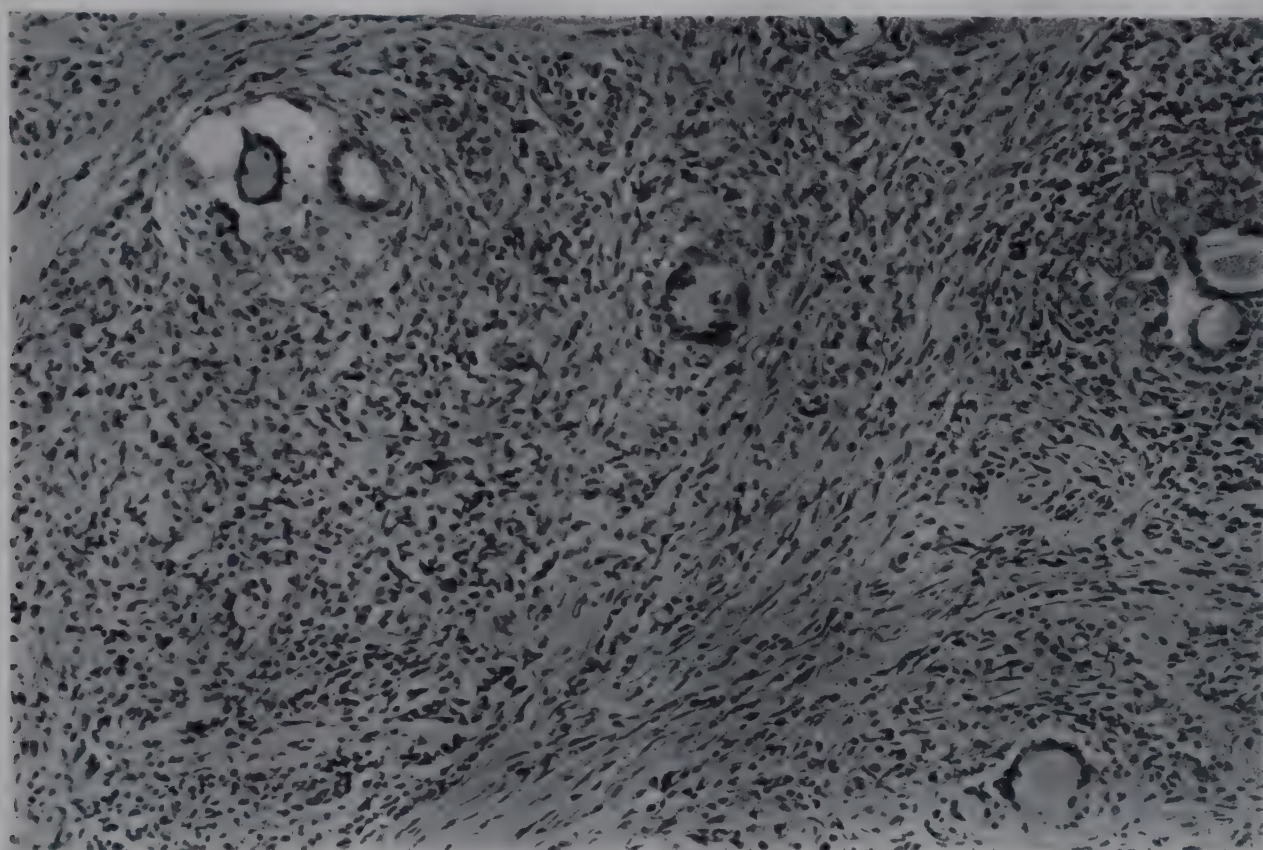


Fig. 406. Struma lymphomatosa. (Armed Forces Institute of Pathology, Neg. No. 75826.)

Small Cell Carcinoma. This is composed of small polyhedral cells with scanty cytoplasm and a hyperchromatic nucleus. There is extensive invasion, and numerous mitoses are seen. The cells may be arranged in columns or islands, as in carcinoma simplex (compact type), or as a more or less uniform infiltration of the stroma (diffuse type) (Fig. 405, *C*). The latter should not be confused with chronic thyroiditis or with malignant lymphoblastoma.

Giant Cell Carcinoma. Because of the atypical appearance of the cells, this type is often erroneously called "carcinosarcoma" and "spindle cell sarcoma." It is a characteristic tumor of women over fifty, and usually starts in a preexisting adenoma. There are numerous tumor giant cells, along with other cells, some polygonal, typically epithelial, and others

fetal, and microfollicular—appear to undergo the transformation more frequently (Coller).

Incidence. Prognosis. Carcinoma of the thyroid is a disease of older persons, with the peak incidence in the sixth decade. In untreated patients, the survival time varies from a few months to several years. Five-year survival percentages after surgical treatment depend on the type of neoplasm: from 60 to 80 per cent with malignant adenoma and papillary carcinoma, and from 20 to 30 per cent with alveolar, small cell, and giant cell carcinoma (Lahey). In a few patients internal irradiation from injected radioactive iodine has been useful in treatment.

Sarcoma. Rarely, tumors of the thyroid are composed of spindle cells or giant cells and have many resemblances to sarcoma. How-

ever, careful study will usually reveal a transition from a distinct epithelial structure, and it is generally believed that most if not all tumors diagnosed as sarcomas of the thyroid are in reality highly anaplastic carcinomas (Smith).

Struma Lymphomatosa

Pathologic Anatomy. The thyroid gland is slightly to moderately enlarged, firm, and pale gray. The average weight is 90 gm. The acini are small and atrophic, and the cells are

present to regard struma lymphomatosa and Riedel's struma as two distinct entities, and not to assume that the latter is the final stage of the former.

Riedel's Struma

Pathologic Anatomy. The thyroid is enlarged and extremely firm. The normal lobulation is not present, and all or a greater part of the gland is replaced by a dense, white fibrillar tissue. The characteristic features to be seen microscopically are diffuse fibrosis,

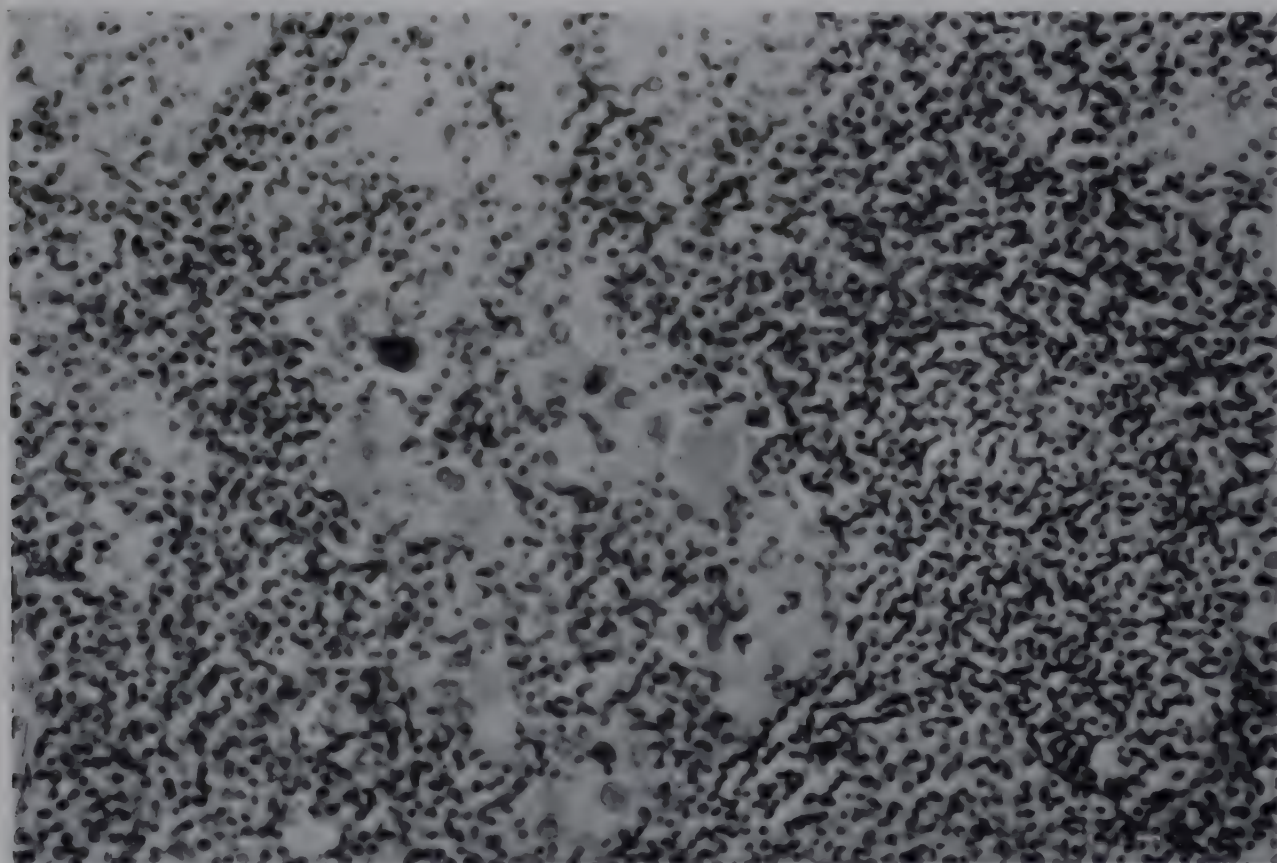


Fig. 407. Riedel's struma. (Armed Forces Institute of Pathology, Neg. No. 75850.)

cuboidal, with central nucleoli. The colloid is scant. The stroma is increased, and there is conspicuous infiltration with lymphocytes and many large lymphoid follicles. The germinal centers may be discernible in the follicles.

Clinicopathologic Correlation. The average age of onset is forty-seven years, and the patients complain of an enlargement of the neck for from one month to five years. The most prominent symptoms are those of pressure on the trachea and other structures of the neck—hoarseness, dysphagia, aphonia, and cough. The basal metabolism varies, but averages slightly more than normal. In about half of the cases the thyroid is adherent by fibrous adhesions to the trachea. The cause is unknown (McSwain and Moore).

Relation to Riedel's Struma. Despite some evidence to the contrary, it seems better at

isolation of a few small acini, and focal and diffuse infiltration with lymphocytes.

Incidence. Causal Factors. The average age of onset is forty years, and rarely do persons less than twenty develop the condition. Women are more frequently affected in a ratio of 4:1. The histologic resemblance to inflammation, together with the chronologic sequence of nasopharyngitis or dental infection and symptoms of Riedel's struma, indicates a cause-and-effect relation.

Atrophy and Fibrosis with Giant Cells. A similar lesion to that of Riedel's struma, except that there are giant cells either isolated or as a part of the granuloma, may be a variant of Riedel's struma or a separate entity. The giant cells are frequently about masses of colloid. The lesion should not be confused with tuberculosis.

Clinicopathologic Correlation. The firm gland of Riedel's struma simulates the picture of carcinoma, especially if there is fixation, as there usually is. Inflammation is the basis of the pain and tenderness (McClintock and Wright).

Myxedema

Myxedema is a chronic deficiency of the thyroid gland, characterized by a diminished

thyroid is enlarged and similar to that of endemic cretinism (Gordon). The cause of the atrophy is not known, but the frequent onset after an infectious disease is suggestive of an initial thyroiditis.

Myxedema of Adults. Myxedema in adults may be associated with atrophy and fibrosis of the thyroid of indefinite causation, or may follow surgical removal of the gland. Under the first condition, the gland is small, firm, and frequently cystic. The chief component is

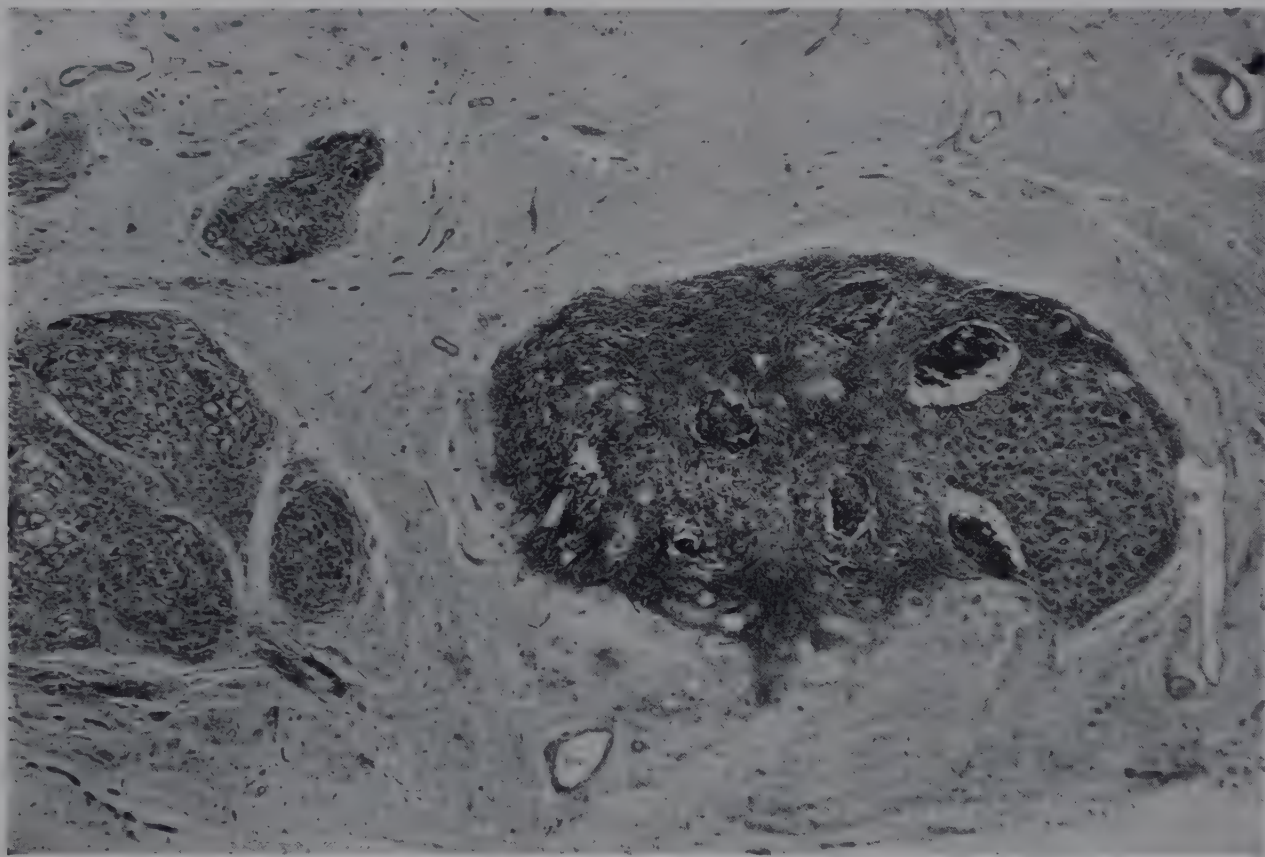


Fig. 408. Thyroid gland in myxedema. (Armed Forces Institute of Pathology, Neg. No. 77406, from material contributed by Drs. Means and Castleman.)

metabolic rate, impaired mentality, an increase in the amount of subcutaneous fat with mucoid infiltration, and other alterations in the subcutaneous connective tissue (Wolf). There are three types: congenital myxedema, myxedema of childhood (sporadic cretinism), and myxedema of adulthood.

Changes in the Thyroid. *Congenital Myxedema.* This is an athyroidism or hypothyroidism caused by agenesis, aplasia, or hypoplasia of the thyroid. There is no thyroid gland in the neck and only small remnants about the foramen caecum. Tissue changes do not appear until after cessation of nursing if the mother has a normally functioning thyroid.

Myxedema of Childhood (Sporadic Cretinism). The usual changes are atrophy and fibrosis of the thyroid. A few alveoli lined by cuboidal cells and filled with a thin colloid are seen in the connective tissue. Rarely, the

a dense connective tissue, infiltrated with lymphocytes and set through with a few small or large acini.

Changes in Other Organs and Tissues. The subcutaneous tissue is atrophic and there is deposited intercellularly, at least in some cases, a thick viscid substance, not chemically identical with mucoid. It appears microscopically as an amorphous, granular or stringy, basophilic deposit. The pituitary is enlarged and well vascularized. The chromophobic cells are relatively increased, and there is an increase of colloid in the cleft. The thymus is atrophic. The adrenal cortex is atrophic and the zona glomerulosa fibrotic. The gonads and secondary sexual organs are small and infantile.

The rate of growth in children is retarded, and the epiphyseal centers are late in appearing. The teeth are also late in erupting.

All muscles are edematous, and mucoid material may be inside the fibers (Fig. 409). The skeletal muscle is lacking in tone, and the person tires easily. The heart dilates and may fail suddenly. Secondary effects of the lesions of smooth muscle are the dilatation of the intestine and constipation. The chromotropic degeneration and rupture of the aorta observed in three patients with cardiac failure incident to hypertension treated by total thyroidectomy may have resulted from the changes in smooth muscle (Kountz and Hempelmann).

Endemic Cretinism

Endemic cretinism is a type of hypothyroidism occurring in those parts of the world where goiter and hyperthyroidism are common.

Changes in the Thyroid Gland. Reports on the thyroid gland in cretins by different investigators are not consistent. Some have observed enlargement in almost every instance, while others state that the gland is smaller than normal in two-thirds. Some reports describe a soft, vascular, colloid-rich

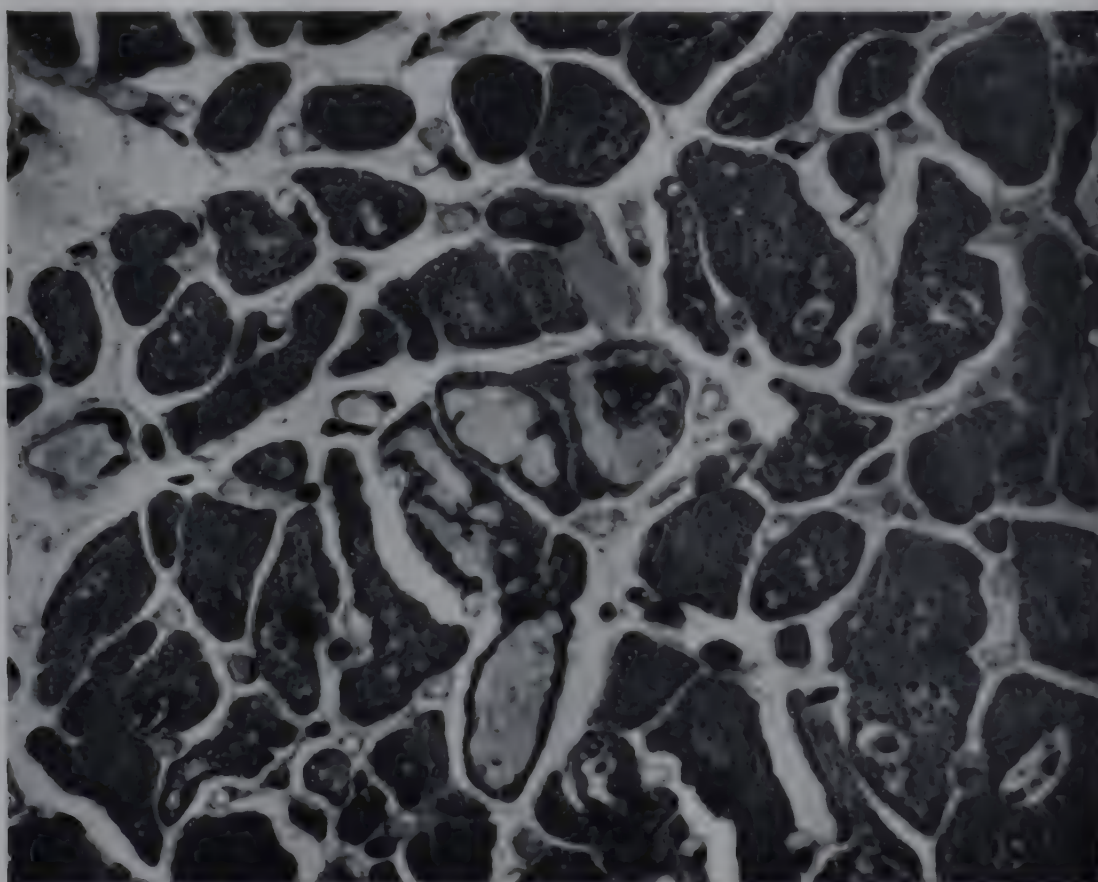


Fig. 409. Mucoid change in striated muscle in myxedema. (Case reported by Foster and Barr, *J. Clin. Endocrinology*, Vol. 5.)

Clinicopathologic Correlation. The clinical signs and symptoms of myxedema are directly or indirectly related to a deficiency of the internal secretion of the thyroid. The rate of metabolism is decreased, so the value for the basal metabolic rate is -20 to -40 . General reflections of this are seen in: retention of water and accumulation of fat, both of which lead to an increase of weight; a low blood sugar value and increased sugar tolerance; increased tolerance to creatine and absence of the normal creatinuria of childhood and of the menstrual cycle; and low body temperature. A similar clinical picture may result from hypofunction of the pituitary (Lerman and Stebbins).

structure of colloid goiter, others speak of foci of hyperplasia reminiscent of hyperthyroidism, and still others call attention to the atrophy and fibrosis of the small firm gland. All observers agree that nodular hyperplasia is present. Either the pathologic changes of cretinism are not constant, or the distinction between endemic cretinism and myxedema of infants has not been sharply drawn.

Changes in Other Organs. The pituitary is enlarged, and there is a relative increase of chromophobic cells. The gonads and the secondary sexual organs are small and atrophic. The maturation with puberty does not occur. The lymphoid tissue throughout the body is

prominent. The bone marrow of the long bones is hypoplastic even in the young child, and the marrow of the trunk contains nodules of lymphoid tissue. The heart is small. The skeletal muscle is atrophic and infiltrated with fat, but the fibers are normally constituted. The brain is of normal size, with slight internal hydrocephalus. Changes in the nerve cells are not well defined. The parathyroids, thymus, and adrenals are normal.

Incidence. Pathogenesis. The exact pathogenesis of cretinism is not known, beyond the fact that simple hypothyroidism is not a complete explanation. It is seen only in those parts of the world where goiter is common, and cretinous children are observed more frequently if one or both parents are goitrous.

Clinicopathologic Correlation. The clinical manifestations are essentially the same as in the other type of hypothyroidism—myxedema. The characteristic facies is dependent on defective development of the bones: protruding zygoma, depressed nasal root, prominent frontal and occipital bosses, enlargement of the mastoid process, and inadequate development of the mandible. The small stature, less than 150 cm. in height, is related to slow growth of the long bones. The teeth are covered by defective enamel, and hence the incidence of dental caries is high. In contrast with the delayed closure of the epiphyses in myxedema, there are irregular skeletal growth, premature union of the epiphyses, and disproportionate skeletal development in endemic cretinism. The almost consistent deafness is related to overgrowth of bone about the labyrinth and ankylosis of the ossicles. There is usually the same depression of metabolism, but some cretins have an elevated basal metabolic rate.

Hyperthyroidism

The disease entity characterized by enlargement of the thyroid, exophthalmos, and tremor (Merseberg triad) has been known by many names: exophthalmic goiter, Graves' disease, Basedow's disease, and Parry's disease.

Changes in the Thyroid. The anatomic appearance of the thyroid is not constant (Graham). In most cases there are hypertrophy and hyperplasia. The gland is enlarged, and

weighs from 50 to 200 gm. The dominant color of the tissue is gray, but vascularity contributes a red color. The organ is firm and the surface distinctly lobulated. Colloid is not visible.

The acini are small and lined by tall columnar cells, which project into the lumens as papillae. The colloid which is present is light-staining, and Anderson's vacuoles and a scalloped edge are prominent features. Between the acini are solid islands of interacinar epithelium, representing hyperplastic buds from preexisting acini (Moritz). The interstitial tissue is not increased, but the blood vessels are numerous and dilated. Distributed irregularly between the acini are small and large nodules of lymphoid tissue.

If the patient has been given iodine in adequate doses, the picture is somewhat different. The acini are larger, and colloid storage is apparent. The cells approach a cuboidal shape, and papillae and interacinar epithelium are less evident. The administration of thiouracil and related compounds results in hyperplasia with a minimum of colloid.

Less commonly, a nodular hyperplasia is observed. The acini between the nodules show the same changes of hypertrophy and hyperplasia (see section on toxic nodular goiter, p. 847).

Changes in Other Organs. The thymus is large, and both the cortex and medulla are well developed. The pituitary is enlarged, with a relative increase of chromophobes. The acidophilic cells are small, and the basophilic cells show degenerative changes. The adrenal glands weigh from 7 to 8 gm., and the cortex is narrow. The gonads are atrophic, and frequently there are changes of hypoplasia in the primary and secondary sexual organs: few primordial follicles in the ovary and sparse sexual hair. The lymphoid tissue is everywhere prominent (Warthin). The heart is enlarged, and in the myocardium are foci of necrosis and fibrosis (Goodpasture). The skeletal muscles are atrophic, and show both fatty degeneration and fat infiltration. The long bones are slender and the cortices thin. In the spongiosa of all bones there is a variable grade of osteoporosis (Bothe, Simpson, and Rowntree). The parathyroids are normal. The liver may show focal necrosis, more widespread necrosis, or cirrhosis (Weller). De-

generative changes in the cervical sympathetic ganglia have been reported.

Exhaustion in Hyperthyroidism. In a few patients who have had hyperthyroidism for many years, the clinical signs point to both hyperthyroidism and hypothyroidism. The gland is firm, and the interstitial connective tissue and lymphoid tissue are prominent. It has been postulated that this is a type of exhaustion. It should be distinguished from struma lymphomatosa.

Biochemical Findings. The thyroid contains only a fraction of the normal amount of



Fig. 410. Enlargement of thyroid gland and exophthalmos in hyperthyroidism. (MacCallum.)

iodine, and the values for blood iodine are increased, averaging 2.7 micrograms per 100 cc. (Davison, Zollinger, and Curtis). Most of the increase is in protein-bound iodine. The administration of radioactive iodine results in active uptake by the thyroid; in fact this may be useful in diagnosis. The glycogen of the heart and skeletal muscle is depleted.

Incidence. Causal Factors. Hyperthyroidism is predominantly a disease of young adulthood and of women (6:1). Examples in children, and in persons over fifty, are unusual (Crile and Crile).

Exact causal factors are unknown. There is some evidence of a constitutional hereditary basis. Even before the appearance of hyperthyroidism, signs of some abnormality of the endocrines may be present (Warthin). Precipitating factors are more definite: severe

emotional strain or shock, trauma, infectious diseases, and overwork under pressure.

Pathogenesis. There is a difference of opinion concerning the primary lesion of hyperthyroidism. In precise studies there is evidence that it is not initially a hyperplasia of the thyroid.

Observations pointing to some activating force in the nervous system are: anatomic changes in the cervical ganglia; precipitation of attack by psychic trauma; and the occurrence of hyperthyroidism after encephalitis (Kennedy, Davis, and Hyslop).

The atrophy of the adrenal cortex, and the similarity of experimental hypofunction of the adrenal cortex and hyperthyroidism, have suggested to some an escape of the thyroid from the antagonistic action of the adrenal cortex.

The known secretion of a thyrotropic hormone by the pituitary has led some to postulate a primary lesion of the pituitary or hypothalamus, but increased amounts of the hormone have never been demonstrated in either the pituitary or the blood.

No one theory may be accepted today, but the preponderance of evidence favors an intimate relation with the nervous system.

Thyroidal Secretion in Hyperthyroidism. A final answer cannot be given on the nature of the hormones of the thyroid. It has been postulated that the hyperplastic gland secretes two substances: an abnormal hormone deficient in iodine, and normal thyroxine. The signs of the disease are thus caused both by dysthyroidism and hyperthyroidism. The former is amenable to therapy with iodine, while the latter is not (Mussey and Plummer). Further study is needed.

Clinicopathologic Correlation. The signs and symptoms result from the presence of a space-consuming lesion in the neck, and the effects of excessive stimulation of other tissues by the thyroidal hormone. The enlarged gland is palpable as a diffuse or nodular mass, and the increased vascularity may produce an audible bruit. The symptoms and signs caused by the excessive secretion are largely those of the increased rate of metabolism: tachycardia, nervousness, palmar sweating, tremor, and hypermotility of the intestine with gastrointestinal symptoms such as anorexia and diarrhea.

Hypoplasia and atrophy of the female sexual organs is associated with amenorrhea in

60 per cent of patients (Gardiner-Hill and Smith). The atrophic and degenerative changes in the skeletal muscles lead to weakness and to a creatinuria similar to that of myasthenia gravis. Since necrosis of the myocardium can be produced experimentally, it may be assumed that it is caused directly by thyroxine. The hepatic necrosis is probably on the same basis.

Exophthalmos. One of the cardinal signs is bilateral exophthalmos (Means). The cause is not known, but appears to be associated with degenerative and inflammatory changes in the extra-ocular muscles (Naffziger and Jones), possibly from overstimulation of the sympathetic fibers (Fig. 410).

Crises in Hyperthyroidism. An occasional patient with hyperthyroidism shows a fulminating syndrome of acute symptoms, especially after thyroidectomy. The outstanding changes are extreme nervousness and hyperpyrexia, rapidly passing to coma and death within a few hours. The cause is obscure. Hyperadrenalism has been suggested (Goetsch and Ritzmann). The most prominent anatomic change is hepatic necrosis, but it is not certain whether it is cause or effect.

Prognosis. Removal of the greater part of the hyperplastic thyroid may be expected to give alleviations of most symptoms in about 80 per cent of patients. The remaining 20 per cent have residual symptoms which may require a second operation. The mortality after thyroidectomy in the better clinics is between 1 and 2 per cent.

Toxic Nodular Goiter

The thyroid gland in some patients with hyperthyroidism shows the picture variously termed "nodular hyperplasia" and "adenoma of the thyroid." The signs and symptoms are less striking than those of the hyperthyroidism of Graves' disease, but do not differ qualitatively. Patients with transition stages between the two conditions are observed.

Following the lead of a few distinguished investigators, many clinicians established a separate disease entity—toxic nodular goiter or toxic adenoma. Morphologic studies of hyperplastic nodules from those with and without hyperthyroidism fail to reveal any constant difference, and no incontrovertible evidence can be secured that the nodules are capable

of function. On the other hand, study of the thyroidal tissue between the nodules in most instances shows hyperplasia such as is seen in Graves' disease.

There is a growing conviction that the toxic nodular goiter is usually a mild manifestation of hyperthyroidism caused by the same mechanism as in other types, and that the nodules are incidental lesions which do not participate in the physiologic disturbance.

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XCVI

Diseases of the Adrenal Glands

The adrenal gland is in reality a triple organ composed of a central medulla, an intermediate androgenic zone, and a peripheral interrenal zone. The chief cell of the medulla—the chromaffin cell—is derived from the neural crest; diseases of the medulla are discussed in the chapter on diseases of the peripheral nervous system (p. 963). The androgenic zone in man is most conspicuous during fetal life, but may in childhood or adulthood give rise to hyperplasia or neoplasia with secondary functional changes. The interrenal zone is common to most vertebrates, and secretes the life-preserving steroids of the adrenal.

Congenital Anomalies. Complete absence of one or both adrenals is a rare anomaly. Hypoplasia in the anencephalic monster is well recognized (p. 583). Not uncommonly, the adrenal is embedded beneath the capsule of the liver or kidney (Weller). Small nodules of androgenic tissue, up to 1 mm. in diameter, are present in the broad ligament or about the testes in over 50 per cent of all newborn infants. Accessory nodules of either androgenic or interrenal tissue are seen throughout the retroperitoneal tissues.

Neonatal Involution. Toward the end of the second week after birth the inner two-thirds of the adrenal cortex appears as a soft red tissue, and the entire gland is decreased in size. There are extreme congestion, slight hemorrhage and fatty degeneration, and necrosis of the cells. After removal of the dead tissue in a few weeks, the stroma collapses and forms a broad band of vascularized connective tissue between the cortex and medulla. At twelve months the band is narrow, and has embedded in it a few pigmented cortical cells. The cortex gradually regenerates, and by the third year has again attained the weight at birth (Aschoff).

Relation to Pseudohermaphroditism. The

essential nature of neonatal involution is a loss of the androgenic zone of the fetal adrenal cortex. In man this occurs at birth in both sexes, in the male mouse at puberty, and in the female mouse during the first pregnancy. Persistence and hyperplasia of the zone in man is seen in pseudohermaphrodites, especially the male type. It is not certain whether the changes in the adrenals are cause or effect. It is possible that they are analogous to the enlargement of the androgenic zone in male mice castrated early in life (Grollman).

Neonatal Hemorrhage. In a few infants who die during the first few days of life, extensive hemorrhage into one or both adrenals is present. The symptoms point to adrenal cortical insufficiency. While the cause of the hemorrhage is not known definitely, it may be only an exaggeration of the normal involutionary process described in the preceding paragraph, or it may be the result of trauma incident to birth: it is commoner in infants born by breech presentation and in those who are revived with difficulty.

Jaudon has given biochemical and clinical evidence that newborn infants may suffer from temporary cortical insufficiency. Just how this is related to neonatal involution and hemorrhage is not clear.

Changes in and Effects on Systemic Diseases. In many systemic diseases, notably the infections and those associated with debilitation, there are alterations in the cortex of the adrenal. On gross examination the cortex is brown rather than yellow, indicative of a loss of lipid. Microscopically the cells of the zona glomerulosa show a tendency to be arranged in an alveolar or acinic pattern (Rich).

As this edition goes to press there are many reports on the effects of cortisone and ACTH on disease processes. It would be premature to give categorical statements at this time. It

would appear that these two hormones have a profound influence on vascular permeability, which in turn is related to many pathologic conditions and lesions (Mote).

Postmortem Autolysis. A cross-section of the adrenal of a person who has died of infectious disease with hyperpyrexia reveals an outer rim of cortex and a central cavity filled with a brown liquid. Examination of the fluid will show that the medulla is a sequestrum, and the essential change is autolysis of the inner part of the cortex. It is possible that the process begins during the agonal phase.

gray, translucent connective tissue, containing small tubercles. Irregular remnants of both cortex and medulla may be present. Healed lesions are absent. The adjacent lymph nodes are not infrequently caseous.

Primary Atrophy. The adrenals are small and weigh from 1 to 3 gm. They are thin, and on section are seen to be composed largely of the gray, firm medulla, with only occasional peripheral islands of yellow cortical tissue. The cortex is partially or completely destroyed, and there is no remnant of the stratification of the cortical cells except for isolated

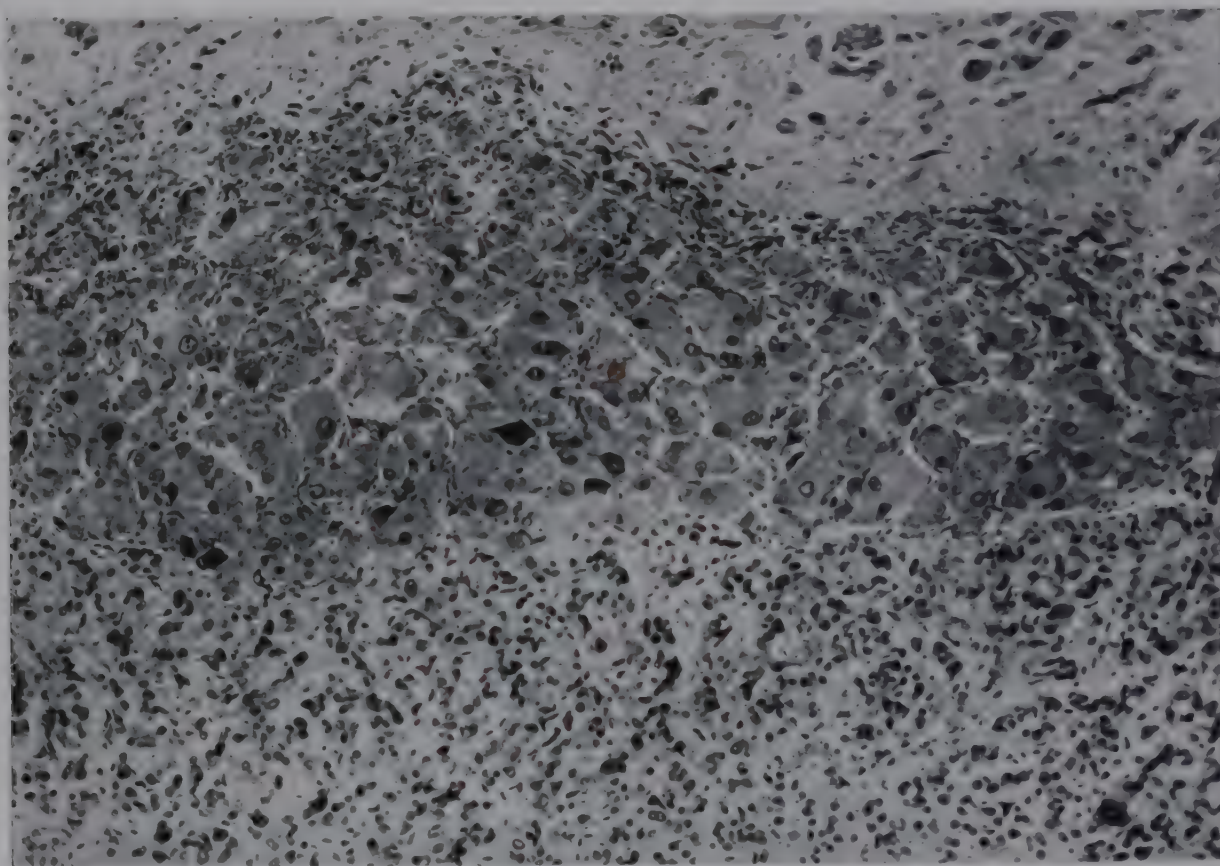


Fig. 411. Remnant of cortex in primary atrophy of adrenal from a patient with Addison's disease.

Addison's Disease

Pathologic Anatomy. Addison's disease is a condition characterized by asthenia, pigmentation of the skin, and gastro-intestinal disturbances, and caused by a destructive lesion of the adrenal glands. In about 70 per cent there is tuberculosis of the adrenal glands, and in 15 per cent the lesion is one known as "primary atrophy" or "cytotoxic atrophy" of the adrenal. In recent years no reports of Addison's disease without some pathologic lesion of the adrenal have been made, such as were published in the older literature (Guttman; Kepler and Willson).

Tuberculosis. The tuberculous lesion is usually of the fibrocaseous type with moderate enlargement of the gland. There are numerous irregular caseous masses surrounded by bluish

columns of the zona reticularis. In the collapsed but not increased connective tissue, vascularization is conspicuous, and there is a moderate diffuse or focal infiltration with lymphocytes. The regenerated cortical cells are large, with bizarre nuclei, and the cytoplasm is poor in fat. The cause of the lesion is entirely unknown (Duffin).

Changes in Other Organs. Anatomic changes in other organs are limited to the skin, cardiovascular system, and the other endocrine glands. The pigmentation of the skin is most marked on the exposed parts of the body and represents an increased deposition of melanin in the basal layer of the epidermis. In a significant percentage the heart is small, and there is an increase of hemofucsin pigmentation of the myocardium. In the pituitary gland there is a relative decrease of basophils, and

those that remain are atypical in that they are large and vacuolated. In the thyroid, especially in association with primary atrophy, there is extensive lymphocytic infiltration of the stroma, formation of lymphoid follicles, and atrophy of the thyroidal epithelium, producing a picture not unlike that of struma lymphomatosa. The thymus in some cases is atrophic and in others is large and prominent. In the latter instances the lymphoid tissue generally over the body is also conspicuous.

Biochemical Findings. Insufficiency of the hormonal activity of the interrenal cells is reflected in changes in the blood; an increase of cholesterol, nonprotein nitrogen, and potassium; and a decrease in chloride, sodium, glucose, and hydrogen ion concentration. There is excessive loss of water through the kidneys without a concomitant increased thirst, so there is a negative water balance. The initial damage leading to these biochemical changes appears to be renal injury and loss of water, sodium chloride and other threshold substances in the urine (Clinton and Thorn). The subsequent shifts of water and electrolytes from tissue to blood account for the other alterations. The hypoglycemia is related to decreased storage of glycogen in the liver and muscle.

Excessive replacement therapy may lead to hypopotassemia, lesions of the myocardium, and cardiac failure (Goodof and MacBryde).

Incidence. Addison's disease occurs in adult life between the ages of fifteen and fifty-five, with the highest incidence in the fourth decade. There is no significant difference in the ages of those with tuberculosis and those with primary atrophy, but in the former there is a slight sex preponderance in men, and in the latter in women. All races are susceptible, but reports in Negroes are uncommon. At times Addison's disease seems to follow some severe mental shock or stress.

Clinicopathologic Correlation. The average duration of life if the disease is untreated is thirteen months in the tuberculous type and thirty-four months in the atrophic type, but periods up to five and ten years are reported. The age of onset has no significant effect on life expectancy. If pigmentation is the initial sign, the outlook is more favorable than if weakness is first noticed: forty-three months as compared to eight months. Further, the deeper the pigmentation the longer the sur-

vival. There are no differences in the symptoms of those with tuberculosis and those with atrophy, so it must be assumed that the signs and symptoms result from destruction of the cortex. Tuberculosis of other organs is usually minimal and does not influence the course. The hypochromic anemia and relative lymphocytosis are difficult to explain (Loeb; Kendall).

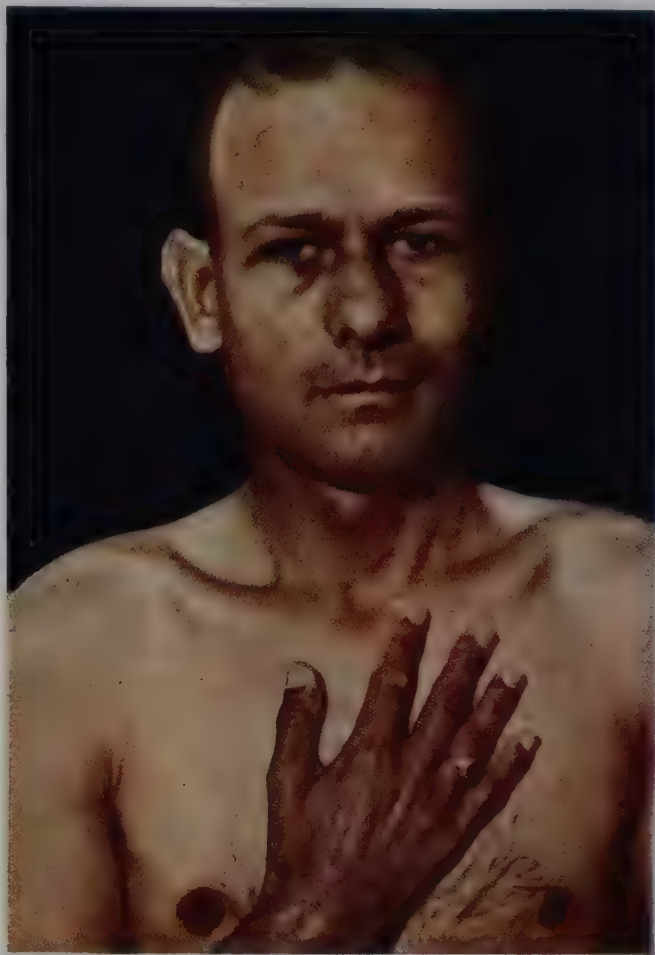


Fig. 412. Addison's disease.

Hyperplasia and Neoplasia of the Interrenal Cells

Pathologic Anatomy. One adrenal undergoes hypertrophy after removal or destruction of the other. In some infections the adrenals undergo hypertrophy, perhaps in response to increased demands for the steroid hormones (Broster and Vines).

A sharp distinction between accessory cortical nodules, focal hyperplasias, and true adenomas cannot always be made. In all there is either within the capsule or within the cortex a circumscribed but not always encapsulated nodule of large cortical cells. The pattern of sinusoid and cortical column is not definite or is totally obscured. The cells are slightly atypical, and have large chromatic nuclei. With larger nodules the encapsulation is definite, the architectural pattern and the cytologic

appearance are more atypical, and the term "adenoma" may rightly be applied. A rare neoplasm with distinct anaplasia is malignant and metastasizes (Geschickter).

Incidence. The frequency of focal hyperplasia and adenoma of the adrenal cortex is in direct ratio to the exactness of criteria and examination. Most adrenals contain some type of spherical mass. Grossly demonstrable nodules are present in about 10 per cent of all adults.

it is possible to relate these changes in the cells of the reticular zone (Blackman). Clinically, two types are recognized, juvenile and adult.

Juvenile Type. The condition, commoner in girls, is characterized in this sex by excessive growth of the secondary sexual hair, hypertrophy of the labia, and enlargement of the clitoris. The ovaries and uterus may be enlarged, but there is no menstruation. In boys there are hypertrichosis, enlargement of the



Fig. 413. Downward displacement of right kidney by a tumor of the right adrenal gland. (Radiograph by courtesy of Dr. Sherwood Moore.)

Significance. Since patients with hyperplasia or neoplasia of the interrenal cells do not show the changes which might be expected with excessive secretion of the steroids of the cortex, it must be concluded that these cells are non-functional. There is no established relation of focal hyperplasia and adenoma of the adrenal to hypertension (Cahill, Melicow, and Darby).

Hyperplasia and Neoplasia of the Androgenic Cells: Adrenogenital Syndrome

The relation of tumors of the adrenal to disturbances in the secondary sexual characters was recognized early. With modern knowledge

external genitalia, excessive muscular development, and deepening of the voice. The testes are not enlarged, and there is no spermatogenesis. The prostate and vesicles are well developed.

The adrenals show all variations from simple hyperplasia, through adenoma, to carcinoma with widespread metastases. The cells are large, round or polygonal, with either a dense or a richly vacuolated cytoplasm and a small dark or light nucleus. With special stains there are frequently distinctive fuchsinophilic granules in the cytoplasm. Not infrequently, the opposite adrenal is congenitally absent—a point to consider in selection of a surgical procedure for cure.

The juvenile form of the adrenogenital syndrome should be differentiated from true precocious puberty. Precocious puberty is usually related to tumors of the region of the pineal (see p. 881) and interstitial cell tumors of the gonads (see p. 894).

Adult Type (Adrenal Virilism). Adrenal virilism or adrenal hirsutism is a condition occurring only in women, most frequently during adolescence or at the menopause. It is characterized both by defeminization and masculinization. Defeminization is seen in cessation of menstruation, atrophy of the secondary sexual organs, atrophy of the ovaries, and formation of ovarian cysts. Masculinization is marked by hypertrichosis, development of the masculine contour of the body and muscles, hypertrophy of the clitoris, and deepening of the voice.

In most patients there are unilateral or bilateral adenomas, occasionally a carcinoma, of the adrenals. The cellular types are similar to those in the juvenile type, and the fuchsino-philic granules can be identified. Removal of the tumor is followed by spectacular return of feminine characteristics (Walters, Wilder, and Kepler; Talbot, Butler, and Berman).

Feminization in Men. A few tumors in men associated with feminization have been reported. Fuchsinophilic granules are not present in the cells. Careful study of other cases is needed to establish the relation between the adrenal and the feminization (Armstrong and Simpson).

Hormonal Aspects. In the adrenogenital syndrome the urine contains excessive amounts of 17-ketosteroids (Warren).

Adrenal Insufficiency with Hypertrophy of Adrenals in Infants. Young infants, especially during the neonatal period, may show signs and symptoms of either intestinal obstruction or of renal insufficiency, in association with immense hypertrophy of the adrenal glands, the two together weighing from 16 to 25 gm. There is a definite cortex and medulla, but within the cortex there is not the sharp distinction between the three zones; and the zona glomerulosa is almost entirely lacking. Occasionally, this adrenal hypertrophy is associated with pseudohermaphroditism, but in most instances the secondary sexual organs are normal and the sex male.

In another type there are precocious development of the secondary sexual organs and

hyperplasia or neoplasia of interstitial or adrenal cortical cells in the testes (Dijkhuizen and Behr).

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XCVII

Diseases of the Pituitary Gland

The pituitary gland is formed by a glandular component (anterior lobe, pars distalis) derived from an evagination of the pharynx known as "Rathke's pouch," and a neural component (posterior lobe, processus infundibuli) attached to the hypothalamus. Between the two is glandular tissue, the pars intermedia, and about the stalk, the pars tuberalis, both of which are derivatives of Rathke's pouch. At birth the entire gland weighs about 100 mg. It increases rapidly in early childhood and then more slowly until the adult size is reached. There are significant correlations between the weight of the anterior lobe and age, sex, stature, and pregnancy.

Secondary Changes in the Cells of the Anterior Lobe

Addison's Disease. In most but not all cases of Addison's disease there is a decrease in the number of basophils, and those that remain are degenerate or vacuolated (Crooke and Russell).

Pregnancy. In pregnancy there is a progressive enlargement of the pituitary gland so that it weighs from 100 to 200 mg. more than in the nulliparous state. Involution is never complete, and the increase in size is more marked in multiparas than in primiparas. Many of the chromophobes increase in size, and a few acidophilic granules appear in the cytoplasm—pregnancy cells (Erdheim and Stumme).

Castration. In both animals and man, castration is followed by hypertrophy of the pituitary. The basophilic cells are large and prominently vacuolated. Many chromophobes with a few basophilic granules appear, to represent transitional forms between these two (Biggart).

Thyroidectomy. Thyroidectomy in animals results in a loss of acidophils and change in

the basophils similar to those of castration (Severinghaus, Smelser, and Clark).

Hyperthyroidism. In patients with Graves' disease there are a decrease in the number of eosinophils, and pyknosis, degranulation, and vacuolation of the basophils (Kraus). In animals given thyroid, the acidophils are prominent, with brilliant granules and hypertrophic Golgi apparatuses and mitochondria. The basophils, rather paradoxically, show the same changes as after thyroidectomy (Kraus).

Chorio-epithelioma and Teratoma. The changes in the pituitary in patients with chorio-epithelioma of the uterus or with functional teratoma of the testis are identical with those in pregnancy. This would indicate that the changes in the pituitary are the result of excessive stimulation by chorionic gonadotropin (Heidrich, Fels, and Mathias).

Lesions of the Posterior Lobe

Few significant lesions of the posterior lobe have been described. Despite the presence of fibroblasts, blood vessels, nerve fibers, and pituicytes (modified glial cells), no undoubted primary tumor has been reported (Bailey). Histologic lesions, none of clinical significance, include cysts, choristoma, dystopia and basophilic invasion.

Cysts. Small cysts lined by ciliated columnar cells are probably ependymal in origin and remnants of the infundibular cavity.

Choristoma. These are small nodules of closely packed large, oval or polygonal, cells with an eccentric small hyperchromatic nucleus and a finely granular basophilic cytoplasm. The cell is probably an atypical pituicyte.

Dystopia. Occasionally, the posterior lobe does not come into intimate contact with the anterior lobe, but is suspended from it by a

pedicle. The condition should not be confused with a tumor of the stalk.

Basophilic Invasion. With increasing age there is an increasing invasion of the posterior lobe by the basophilic cells of the pars intermedia. Cushing suggested that this represents a hyperactivity of the posterior lobe, and that it forms the histopathologic basis for eclampsia and hypertension, but many others have failed to substantiate this claim (Parsons).

Lesions of the Pars Intermedia

No definite clinical syndrome has been related to the pars intermedia. It increases in weight with age, probably as the result of an increase in the basophilic cells.

Nonclinical Type. Routine study of the pituitary gland by step sections shows a significant number of small spherical nodules. Parsons designates those nodules which cause compression or realinement of the surrounding structures as “nodular hyperplasia,” and reserves the term “simple hyperplasia” for nodules without change in the contiguous tissue. His observations on the incidence of these lesions is typical, and is shown in Table 49. The nodules are located in all parts of the gland, but the basophilic type tends to occur in the peripheral zone. The cells are identical with those in the normal pituitary. Erdheim describes focal hyperplasia composed of pregnancy cells. The significance of the basophilic adenoma is not definite. In most patients there

TABLE 49. OCCURRENCE OF SIMPLE HYPERPLASIA AND NODULAR HYPERPLASIA IN RELATION TO CELLULAR TYPE—107 PITUITARIES

Cellular Type	Simple Hyperplasia		Nodular Hyperplasia	
	Women	Men	Women	Men
Acidophilic.....	0	0	0	0
Basophilic.....	5	7	3	2
Chromophobic.....	7	2	0	6
Two nodules of different types.....	4	1	0	0
Mixed.....	4	7	3	5
Totals.....	20	17	6	13

Colloid Storage. In some pituitaries there is from a slight to an excessive storage of a colloidlike substance in the residual lumens of the pars intermedia. The significance of this is unknown, and there is no correlation between the amount of colloid and the number of epithelial cells.

Cysts. Rare cysts of clinical importance apparently arise in the pars intermedia. The lining cell may be squamous, cuboidal, columnar, or ciliated columnar (Frazier and Alpers). Similar ciliated epithelial cysts of the anterior lobe have been reported (Parsons).

Tumors of the Anterior Lobe

On histologic grounds it is not always possible to distinguish between nodular hyperplasia, adenoma, and carcinoma of the cells of the anterior lobe. The best approach seems to be to divide all nodules into two types, nonclinical and clinical.

is no demonstrable clinical correlation, but in a few there is Cushing’s syndrome (p. 861).

Clinical Type. Large, clinically manifest adenomas of the pituitary constituted 17.8 per cent of the 2023 verified intracranial tumors of Cushing. A large adenoma of basophilic cells has not been reported, but there are acidophilic types, chromophobic types, and mixed types. The chromophobic constitutes about 70 per cent of all.

Pathologic Anatomy. Adenomas are thinly encapsulated, soft, gray tumors, completely filling the sella or extending upward into the suprasellar space. If the capsule is broken, as it usually is in large tumors, there is invasion of the brain or bone by a fleshy, reddish gray tissue (Kraus). Similar tumors have been reported in the substance of the sphenoid bone (Erdheim) and in the nasopharynx (Lee-gaard).

The cells of the *chromophobic adenoma* are elongated or polygonal, and have a distinct

perivascular arrangement. Connective tissue septa divide the cells into solid nests without acinic orientation. The nuclei are oval and hyperchromatic, and the cytoplasm is finely granular.

The *acidophilic type* is composed of large sheets of round or polygonal cells, with abundant cytoplasm filled with specific granules, and a vesicular nucleus. Multinucleated cells are common. The stroma is delicate.

The *mixed type* contains both chromophobic and acidophilic cells, with a tendency of

Tumors of the Hypophyseal Stalk

About the stalk attaching the posterior lobe to the hypothalamus there are, in over half the population, one or more small masses of epithelial tissue derived from Rathke's pouch, known as the "pars tuberalis." Cysts and tumors may be derived from these rests.

Pathologic Anatomy. The gross appearance varies from a smooth, thin-walled, unilocular or multilocular cyst, to a lobulated, firm, solid tumor. There are frequently combinations of



Fig. 414. Tumor of the hypophyseal stalk.

the latter to be located in the peripheral parts of each lobule.

Whether or not some tumors are carcinomas is largely a matter of definition. Some invade surrounding structures and have numerous cells in mitosis, and implantation and distant metastases have been observed in a few cases (Cushing).

Significance. The true acidophilic adenoma is closely associated with acromegaly (p. 863). It is said that mixed adenoma with prominent acidophilic elements may give changes suggestive of acromegaly (Dott and Bailey). The chromophobic adenoma has no demonstrable function and is important only as a space-consuming lesion (p. 858).

Tumors in Animals. Similar adenomas of the pituitary of rats have been studied (Saxton).

the solid and cystic structure. Since the origin is at a point above the sella, most cysts and tumors are suprasellar.

Cysts. The cysts are lined by stratified squamous epithelium which shows extensive keratinization. The cavity is filled with a thick grumous fluid, rich in cholesterol, derived from the breakdown of the epithelial cells. At some points the epithelial continuity may be interrupted, and crystals of cholesterol may lie free in the fibrous tissue wall; hence the synonym of "cholesteatoma." Calcification and ossification of the wall are common and serve as an important diagnostic sign of "suprasellar cyst" in a radiograph. Embedded in the fibrous tissue may be small islands of squamous epithelium, but rarely any specialized epidermal structures.

Solid Tumors. These have two types of

epithelium in a fibrous stroma: epidermoid and ameloblastic. The epidermoid cells are of the usual sort, with typical intercellular bridges and keratinization. The ameloblastic cells are arranged as primitive enamel organs with peripheral columnar enamel epithelium and centrally placed enamel syncytium. Within the

persists in at least 95 per cent of persons. It is located in the deeper parts of the mucosa just posterior to the vomer and just anterior to the adenoid. The chief cell is undifferentiated epithelium, but typical cells of the anterior lobe may be present. Lesions of it are poorly understood (Melchionna and Moore).

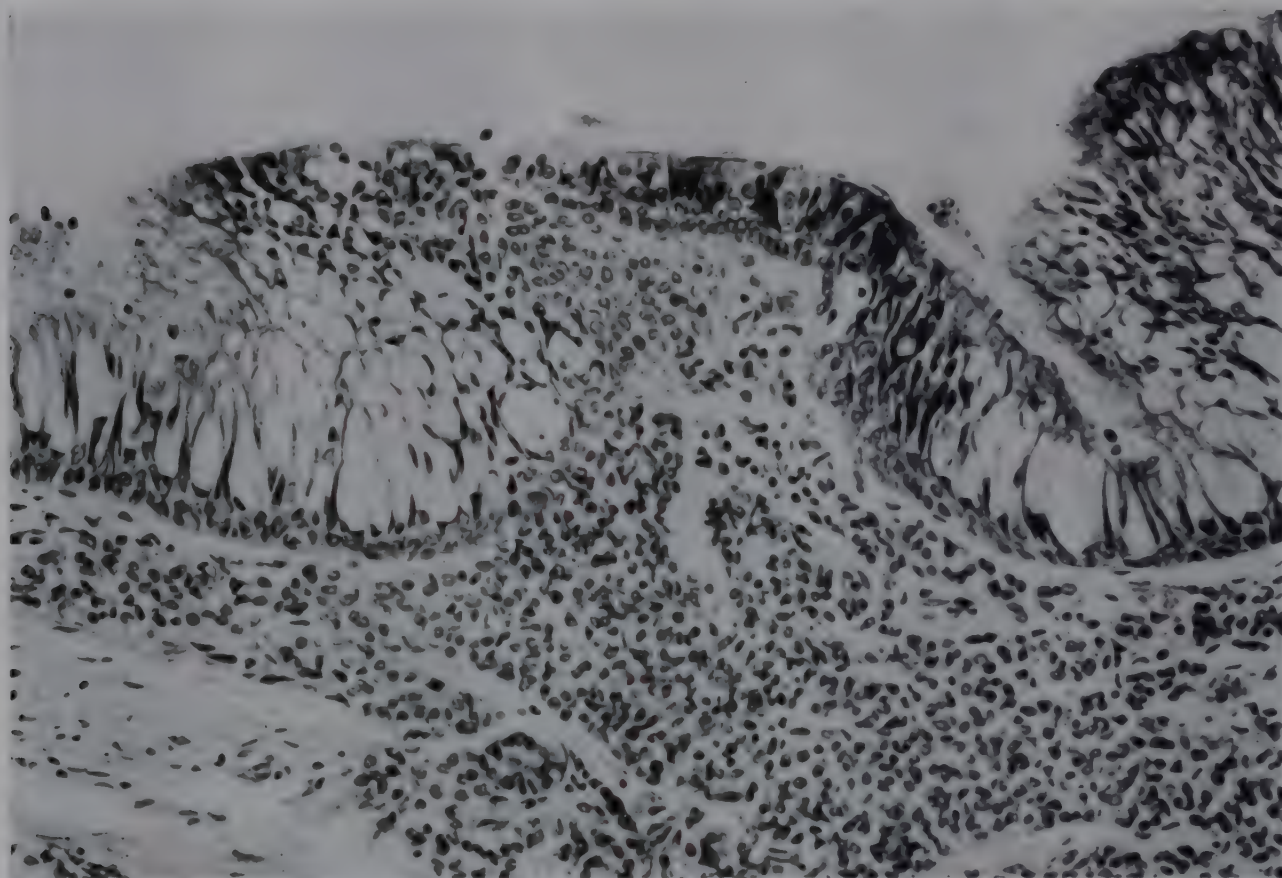


Fig. 415. Pharyngeal pituitary. (From the material reported by Melchionna and Moore. Am. J. Path., Vol. 14.)

syncytium differentiation into epidermoid pearls is common (Conley).

With continued growth of either the cysts or solid tumors, there is compression of the hypothalamic region and at times invasion of the third ventricle. The anterior and posterior lobes may be compressed into the base of the sella (Erdheim).

Incidence. Cysts and tumors of the stalk may occur at any age, but are commonest in children and young adults. There is no preponderance in one sex.

Pituitary Infantilism. Intracellular Cysts. Pituitary infantilism or nanosomia is a syndrome caused by complete destruction of the anterior lobe early in life. There is a cessation of growth, but the epiphyses do not unite. The gonads and secondary sexual organs remain undeveloped. The commonest cause is an intracellular cyst, since this lesion destroys the pituitary but does not endanger life (Erdheim).

Pharyngeal Pituitary. At the lower end of Rathke's pouch a small nodule of tissue also

General Effects of a Space-Consuming Lesion in the Region of the Sella

All large cysts and tumors of the anterior lobe and of the stalk give a characteristic clinical picture dependent on four basic effects: (1) pressure on neighboring structures, (2) general increase of intracranial pressure, (3) changes related to secretory activity of the neoplastic cells, and (4) changes caused by secondary effects on other endocrine glands (Cushing).

Pressure on Neighboring Structures. The pituitary is close to many important structures, and pressure on them gives rise to signs and symptoms. As the tumor expands in the anterior lobe, it fills the sella and presses against the bone and covering dura. The clinoid processes are thin and quickly undergo atrophy: a change easily seen in a radiograph and diagnostic of a sellar tumor of some sort. Pressure on the dural roof of the sella may be the cause of "pituitary headache." When the tumor rises out of the sella, it comes in contact with the

hypothalamus and the optic chiasm. Interruption of certain pathways from the hypothalamus to the posterior lobe or pressure atrophy of certain nuclei about the third ventricle may result in adiposogenital dystrophy (p. 861) or the hypothalamic syndrome (p. 859). Compression of the optic nerves leads to atrophy and a typical bitemporal hemianopsia.

General Increase of Intracranial Pressure. The tumors are space-consuming lesions

if the secretions are abnormal or excessive, there are corresponding alterations in the anatomic structure and function of the thyroid, parathyroids, adrenals, and gonads. In acromegaly with excessive secretion of the acidophilic cells, there are enlargement and nodule formation in the first three. In hypofunction there is atrophy of all, with a concomitant atrophy of the secondary sexual organs.



Fig. 416. Expansion of the sella by a tumor of the pituitary. (Radiograph by courtesy of Dr. Sherwood Moore.)

within the cranial cavity, and produce all the changes associated with increased intracranial pressure (Chapter CV, p. 930). Occasionally, there is invasion or compression of the third ventricle with resultant bilateral internal hydrocephalus of the lateral ventricles.

Secretory Activity of the Neoplastic Cells. The acidophilic cell secretes an excessive amount of hormones which produces acromegaly (p. 863). Some basophilic adenomas are related to Cushing's syndrome (p. 861). Intracellular cysts or growth may cause compression atrophy of the pituitary and the secondary changes of hypopituitarism, for example, nanosomia (p. 858).

Secondary Effects on Other Endocrine Glands. The other endocrine glands are in large part dependent on the activity of the pituitary. If it is destroyed by compression, or

Hypothalamohypophyseal System: The Hypothalamic Syndrome

Investigators during the nineteenth century and the early part of the twentieth century noted that some lesions in the region of the pituitary were associated with one or more of five clinical signs and symptoms: hypersomnia, polyuria, genital atrophy, obesity, and disturbance in thermal regulation. These changes were variously attributed to the posterior lobe of the pituitary, to the anterior lobe of the pituitary, and to the hypothalamus.

Anatomy of the Hypothalamus. The nuclear masses of the hypothalamus may be divided into two categories: those in the diencephalic region and in the wall of the third ventricle, and those in the region of the mammillary bodies. The details of these are given in Fig.

417. Further careful correlative studies may well elucidate the complex relations between the hypothalamus, the pituitary, and many bodily functions.

supra-opticohypophyseal tract. Any lesion destroying these nuclei or interrupting the tract will depress the antidiuretic processes, and increased amounts of water will be excreted by

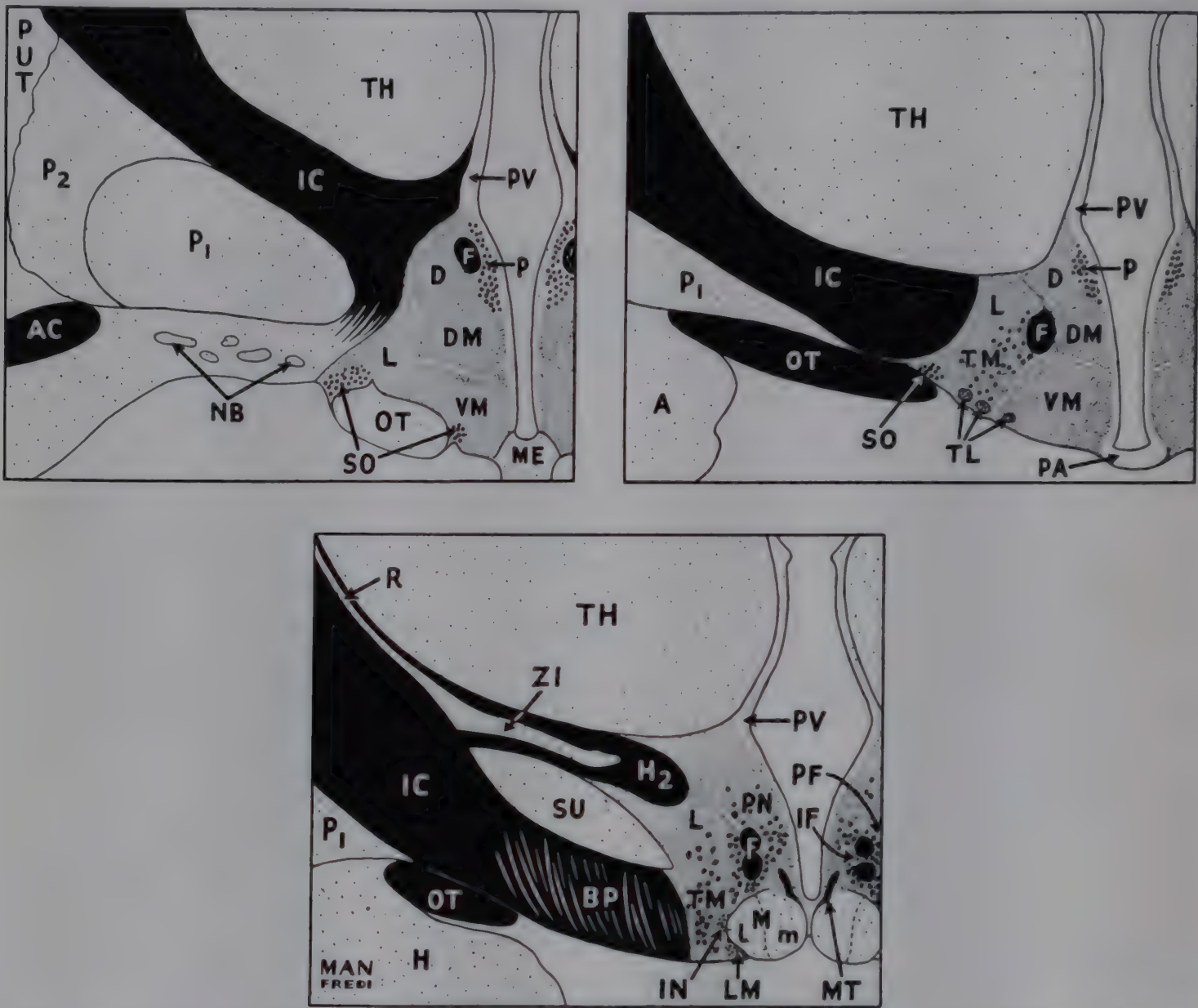


Fig. 417. Diagrammatic representation of the hypothalamic nuclei. Three coronal levels are illustrated: the infundibular, the midtuberal, and the mammillary. Adjacent to the ependyma of the third ventricle is the internal periventricular system (PV), which in the midtuberal region is contiguous with the nucleus periventricularis arcuatus (PA). In the medial portion of the hypothalamus are the paraventricular (P), dorsal (D), dorsomedial (DM), ventromedial (VM), and posterior (P) nuclei. Extending diffusely throughout the lateral hypothalamic region (L) is the tuberomammillary nucleus (TM); the collection of cells of the tuberomammillary nucleus which partly surrounds the fornix (F) is known as the perifornical nucleus (PF), and that which interdigitates it, the interfornical nucleus (IF). Surmounting the optic tract are two divisions of the supra-optic nucleus (SO). Bulging from the lower surface of the hypothalamus are the nuclei tuberis laterales (TL). The medial mammillary nucleus (M) is divided into lateral and medial components (l and m). Lateral to it are lateral mammillary nucleus (LM) and the nucleus intercalatus (IC). Other structures are designated as follows: A, amygdala; AC, anterior commissure; BP, basis pedunculi; H, hippocampus; H₂, field H₂ of Forel; IC, internal capsule; ME, median eminence; MT, mammillothalamic tract; NB, nucleus basalis; P₁ and P₂, internal and external divisions of the globus pallidus; PUT, putamen; R, reticular nucleus; TH, thalamus; ZI, zona incerta. (From Haymaker and Papez: *The Hypothalamus*. Charles C Thomas, 1947, through the courtesy of Dr. Webb Haymaker.)

Water Metabolism. Diabetes Insipidus. It appears that the anterior lobe of the pituitary elaborates a principle that stimulates diuresis, and that the posterior lobe secretes a principle that is antidiuretic—puitritin. Regulation of the antidiuretic substance is mediated by impulses from the supra-optic nuclei over the

the kidney—polyuria. There will be a secondary corresponding increased ingestion of water—polydipsia (Ranson, Fisher, and Ingram). **Thermal Regulation.** Neither experimental studies (Bazett, Alpers, and Erb) nor studies in human beings (Davison and Selby) have

been entirely satisfactory in explaining disturbances in thermal regulation, but destructive lesions just cephalic to the mammillary bodies seem to be related to a loss of this ability.

Hypersomnia. Observations of narcolepsy in patients with lethargic encephalitis, with tumors of the pineal body, and with tumors of the third ventricle, and the association of hypersomnia with oculomotor disturbances, point to a localization of centers related to sleep in the wall of the posterior part of the third ventricle and the adjacent aqueduct of Sylvius and thalamus (Fulton and Bailey).

Adiposogenital Dystrophy

Adiposogenital dystrophy, or Fröhlich's syndrome, is characterized by hypogenitalism and pronounced obesity, which cannot be explained on a dietary basis, and in growing children by delayed skeletal development.

Pathologic Anatomy. The obesity has a peculiar distribution, with localized deposits about the hips, upper thighs, lower abdomen, mons veneris, and breasts. The skin is soft and delicate, and there is hypotrichosis. In the male sex there is partial feminization, with large breasts, a horizontal upper line of pubic hair, and a broadening of the hips. In adolescents the external and internal genitalia are small, and in adults atrophy of the sex organs occurs. Functionally, there are loss of libido, amenorrhea, sterility, and frigidity. The prostate and the seminal vesicles, and the uterus and uterine tubes are atrophic and similar to those of a prepuberal person. There is retardation of growth, especially in the long bones, so that the extremities are relatively short (Beck).

Causal Factors. In the original case of Fröhlich there was a chromophobic adenoma of the pituitary. Since then many other lesions have been described: encephalitis of the hypothalamic region (Moore and Cushing), tumor in the region of the third ventricle and infundibulum (Fulton and Bailey), and traumatic lesions of the tuber cinereum just posterior to the pituitary stalk.

Delayed Puberty. In children, the sudden onset of obesity at seven to ten years with delay in the appearance of puberty is frequently referred to as "Fröhlich's syndrome." So far as can be determined, there are no

lesions of the hypothalamus or pituitary, and the condition must be regarded as a physiologic hypopituitarism (Bruch).

Cushing's Syndrome

The outstanding features of Cushing's syndrome, or basophilism, are: a rapidly acquired, peculiarly disposed, and usually painful adiposity, confined to the face, neck, and trunk; kyphosis, with a measurable loss of height associated with lumbosacral pain; sexual dystrophy, shown by early amenorrhea in women and ultimate functional impotence in men; hypertrichosis of the face and trunk in all women, as well as in preadolescent boys, and possibly the reverse in adult men; a dusky or plethoric appearance of the skin, with purplish lineae atrophicae; vascular hypertension; a tendency to polycythemia; and variable backaches, abdominal pains, fatigability, and ultimate extreme weakness (Cushing).

Pathologic Anatomy. Although all the original cases reported by Cushing were associated with a basophilic adenoma of the pituitary, subsequent studies have cast doubt on the cause and effect relation of the two.

There is apparently only one anatomic change which is present in all examples of Cushing's syndrome—a characteristic alteration in the structure of the basophilic cells of the pituitary, known as "Crooke's change." The normal cytoplasm, charged with bright basophilic granules, is replaced by a dense, homogeneous, hyaline cytoplasm, which has a high index of refraction and stains a uniform grayish blue with the Mallory stain. The extent of the hyaline change shows great variation (Crooke).

Other lesions which are probably causally related are hyperplasia or adenoma of the adrenal gland, primary tumors of the thymus, and atrophy of the paraventricular nuclei of the hypothalamus.

In the other endocrine glands there may be hyperplasia or the formation of adenomas. This is especially true in the thyroid and in the parathyroid glands. In most instances there is osteoporosis of the bones, and this cannot be definitely associated with hyperplasia of the parathyroids. The gonads and the secondary sexual organs are atrophic except in tumors of the adrenal in women, in which there is likely to be hypertrophy of the clitoris. The asso-

ciated lesions of hypertension are similar to those in the usual case of cardiovascular renal disease. There are hypertrophy and dilatation of the heart, arteriolar nephrosclerosis, and thickening of the arterioles in all the organs of the body (MacMahon, Close, and Hass).

Pathogenesis. Heinbecker has submitted convincing experimental and morphologic evidence that the basic change in Cushing's syndrome is a dysfunction of the basophilic cells of the pituitary. Further, he has shown that the dysfunction is effected through an unbalanced influence from the adrenal cortex: ex-

Clinicopathologic Correlation. The average duration of life from the onset of symptoms is five years, and for some reason, as yet not explained, there is a greatly increased susceptibility to infection, so that most of the patients die of sepsis. The tumors of the adrenal and pituitary are rarely large enough to produce direct signs and symptoms. The tumors of the adrenal may be demonstrated by roentgenography after injection of air into the perirenal tissues. The tumors of the pituitary in general cause no roentgenologically demonstrable enlargement of the sella turcica. The

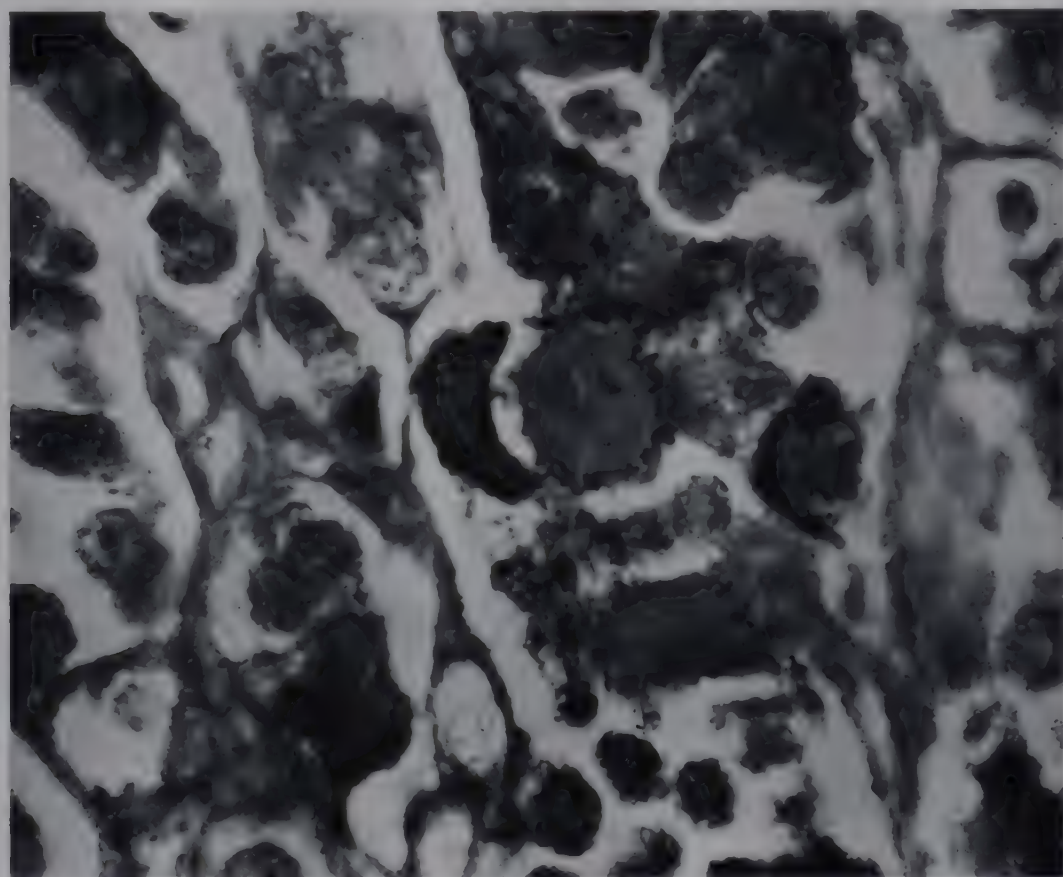


Fig. 418. Crooke's change in basophilic cells of pituitary in Cushing's syndrome.

cessive secretion of the hyperplastic or neoplastic adrenal, or normal adrenal secretion acting on a pituitary sensitized to it because of atrophy of the paraventricular nuclei.

Incidence. Basophilism is commonest in young women. An adrenal tumor is rare in basophilism of adult men; it is the rule in basophilism of children; and it is common in basophilism of adult women. The average age of onset is in the third and fourth decades of life.

Assay of Hormones. In basophilism associated with a tumor of the pituitary there are no demonstrable changes in the urinary excretion of hormones, but with a tumor of the adrenal there is an excessive amount of 17-ketosteroids in the urine, almost entirely dehydroisoandrosterone (Crooke and Callow).

hypertrichosis and other evidences of masculinization with a tumor of the adrenal are probably related to the excessive 17-ketosteroids produced by the neoplastic cells and excreted in the urine.

Laurence-Moon-Biedl's Syndrome

The typical syndrome consists of obesity, hypogenitalism, mental retardation, polydactylism, and pigmentary retinal degeneration (Jaso and Curbelo). In the reported autopsies no characteristic or consistent pathologic changes have been reported. The secondary sexual organs are atrophic. The condition is probably inherited as an autosomal recessive characteristic in two adjacent genes in the same chromosome. An alternative possibility

is that one of the genes is a recessive, sex-linked in the Y chromosome, and the other a dominant, autosomal gene. This latter explanation seems likely because of the preponderance in males in a ratio of 65:35 and the lack of inheritance of the complete syndrome in any one person (Sorsby, Avery, and Cockayne).

features, with a body height of as much as 7½ or 8 feet; in acromegaly the enlargement of the bones is more in a transverse diameter, the lower jaw being large and prominent, the supra-orbital ridges conspicuous, and the hands and feet much larger than normal. This enlargement is caused by hypertrophy and hyperplasia of the fibro-adipose tissue and by



Fig. 419. Acromegaly. Note the narrow chest, large joints, hypotrichosis. Also the large size of the hands compared with those of Dr. Crowe, whose height is 5 feet 8 inches. (Harvey Cushing.)

Acromegaly—Gigantism

Acromegaly and gigantism are essentially the same disease, and represent the results of excessive amounts of the growth-promoting hormone of the pituitary. They differ only in the time of onset: gigantism before the closure of the epiphysis and acromegaly after the closure of the epiphyses.

Pathologic Anatomy. The physical appearance of each is characteristic: in gigantism there is uniform and symmetrical enlargement of all the long bones and of the facial

an increase in the diameter of the bones. In both conditions the lips and tongue are large and the papillae of the tongue prominent. There is splanchnomegaly affecting most of the viscera. The lungs average 1500 gm., the heart 450 gm., the liver 2500 gm., the kidneys 250 gm. each, and the spleen 350 gm.

In every true case of acromegaly or gigantism which has been studied anatomically, eosinophilic cell adenoma of the pituitary has been observed. If this is not present in the region of the sella, it may be within the substance of the sphenoid bone along the path-

way taken by Rathke's pouch. In the other endocrine glands there is nodular hyperplasia. The thyroid varies from 100 to 300 gm., and contains numerous hyperplastic nodules. The parathyroid glands are frequently enlarged, and one or more may show the microscopic appearance of an adenoma. The adrenal glands together weigh from 20 to 40 gm, and show numerous foci of hyperplasia in the cortex. The pancreas averages 140 gm., and the islands of Langerhans are large and conspicuous. The gonads are of normal size or atrophic, and there is in general atrophy of the secondary sexual organs. The ovaries are fre-

complete destruction of the anterior lobe of the pituitary (Farquharson, Belt, and Duff; Escamilla and Lisser).

Pathologic Anatomy. The body is emaciated. The subcutaneous fat is scant and the skin wrinkled. All the organs are small, brown, and firm. This is well shown in the average figures cited by Farquharson, Belt, and Duff for four cases of Simmonds' disease and five cases of acromegaly (Table 50).

The anterior lobe of the pituitary is small and firm. The usual lesion is an absence of the characteristic cells, with fibrosis suggestive of healing of ischemic necrosis. Occasionally,

TABLE 50. WEIGHT OF ORGANS IN SIMMONDS' DISEASE AND ACROMEGALY

	Simmonds' Disease	Acromegaly	Normal
Body weight.....	95 lb.	194 lb.
Heart.....	175 gm.	448 gm.	300 gm.
Liver.....	866 gm.	2462 gm.	1500 gm.
Kidney.....	89 gm.	247 gm.	155 gm.
Spleen.....	144 gm.	353 gm.	200 gm.
Pancreas.....	43 gm.	135 gm.	100 gm.
Thyroid.....	10 gm.	76 gm.	40 gm.
Adrenals.....	6.4 gm.	26 gm.	12 gm.

quently cystic (Cushing and Davidoff). The skin is thickened. There is an increase in the size of the hair follicles, sebaceous glands, and epidermal papillae.

Biochemical Findings. The usual significant changes in function are: hyperglycemia and glycosuria (sometimes indistinguishable from true diabetes mellitus), and an increased metabolic rate. There is sometimes an associated diabetes insipidus (p. 860).

Clinicopathologic Correlation. There are few changes which have not been discussed in the section on general effects of a space-consuming lesion of the pituitary (p. 858). The onset is usually in young adulthood, and the course extends over many years. In some patients progress of the condition ceases after five to twenty years, and this may be associated with degranulation of the cells.

Hypophyseal Cachexia

Hypophyseal cachexia, or Simmonds' disease, is characterized by marked emaciation, weakness and pallor, loss of teeth, loss of axillary and pubic hair, loss of sexual function, and mental disturbances, and is caused by

foci of necrosis are demonstrable (Sheehan). Rarely, there is destruction by tuberculosis (Kirshbaum and Levy) or by tumor (Farber, Goldstein, and Beswick). The posterior lobe is essentially normal. The other endocrine gland shows atrophy but no fibrosis. The gonads and the secondary sexual organs are atrophic.

Incidence. Causal Factors. The fact that most instances of Simmonds' disease are in multiparous women, and that symptoms not infrequently begin after pregnancy, seems significant. It is well known that focal necrosis in the anterior lobe occasionally occurs during the puerperium, and widespread necrosis on this basis is believed to be the initial change (Gotshalk and Tilden). Simmonds spoke of embolism and thrombosis, but this cannot always be demonstrated.

Clinicopathologic Correlation. The clinical changes are exactly what would be expected on withdrawal of all the target hormones of the pituitary. The more evident are the thyrotropic, adrenotropic, and gonadotropic, and they are related to asthenia, anorexia, impairment of mental activity, low basal metabolism, loss of sexual function, and anemia. Replace-

ment therapy has not been satisfactory probably because we do not have complete knowledge of the target hormones (Fraser and Smith).

The course of the disease extends over years, and death may result from exhaustion or intercurrent infection.

Anorexia Nervosa. This syndrome occurs in young women, and is primarily an aversion to eating. After a time there are many resemblances to Simmonds' disease—amenorrhea, emaciation, and low metabolic rate. There are, however, differences, and there are no changes in the pituitary gland (Richardson).

Adiposis Dolorosa

Adiposis dolorosa, or Dercum's disease, is characterized by localized painful adiposity, asthenia, mental disturbances, and ulcers and bullae on the extremities (Foot, Good, and Mènard).

Pathologic Anatomy. Pathologic changes are not constant, but in most instances there are anatomic alterations in the endocrine glands. Fibrosis and focal hyperplasia or neoplasia of the pituitary are seen in most patients. Other lesions are fibrosis of the thyroid, persistence of the thymus, focal hyperplasia of adrenals, and atrophy of the gonads. The subcutaneous deposits of fat are not different histologically from normal fat.

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XCVIII

Diseases of the Insular Tissue of the Pancreas

The first objective evidence that the pancreas had some function other than that of an intestinal gland came with the classic experiment of Von Mering and Minkowski in 1889. These investigators noted that diabetes followed removal of the pancreas in dogs. The relation to human diabetes was first reported by Opie in 1901, who observed hyalinization of the islands in a seventeen-year-old girl with diabetes. The final proof was the isolation of insulin by Banting and Best in 1922.

The islands contain three cellular types—alpha cells, beta cells, and D cells. The beta cell is related to insulin production and changes in its function result in diabetes and hyperinsulinism. The alpha cell probably secretes a hormone producing hyperglycemia, but no disease in man related to it is known.

Diabetes Mellitus

Diabetes mellitus is a disturbance in the utilization of carbohydrate, usually associated with some anatomic lesion of the pancreas.

Pathologic Anatomy. Pathologic changes in a patient with diabetes are in large part determined by whether or not he has received adequate treatment with insulin. The descriptions given here are typical of a person who dies of diabetes without having had adequate therapy.

Pancreas. The pancreas shows few gross pathologic changes. It may be slightly atrophic and firmer than normal. Occasionally the pancreas is firm and rusty brown, and is the seat of typical hemochromatosis. Carcinoma (McKittrick and Root), or the healing of an acute hemorrhagic necrosis (Warfield) or of hemorrhage following trauma (Wells), may occasionally be associated with diabetes.

The commonest microscopic change is hyalinization of the islands of Langerhans. This hyalin first appears as a homogeneous sub-

stance within the cells of the islands, and gradually increases with atrophy and loss of the cells. It is commoner in older people (Ahronheim; Arey). The second commonest microscopic alteration of the islands is fibrosis, in which fibroblasts with a moderate amount of collagen replace the cells of the islands. In children the islet cells may be well preserved but infiltrated with lymphocytes (Warren). Hyperplasia of the cells of the islands, either in diffuse form or in a columnar

TABLE 51. FREQUENCY OF PATHOLOGIC CHANGES IN PANCREAS IN DIABETES MELLITUS

Type of Change	Number of Cases	Percentage
Normal.....	168	19.9
Hyalinization of the islets...	299	35.5
Fibrosis of the islets.....	282	33.5
Hyperplasia.....	79	9.4
Hydropic degeneration.....	22	2.6
Pyknotic nuclei.....	21	2.5
Hemochromatosis.....	18	2.1
Lymphocytic infiltration....	15	1.8

arrangement, is not infrequently observed. In about 20 per cent of all patients with diabetes it is impossible to demonstrate any pathologic change in the pancreas. The frequency of the different changes is well shown in 842 cases collected by Warren (Table 51).

Warren studied the pancreas in 200 non-diabetic persons, and found fibrosis of the islands in 15, hyalinization in 4, hypertrophy in 5, pyknotic nuclei in 2, and hydropic degeneration in 2.

Less commonly there may be quantitative changes in the number of islands; histological study of the number of islands indicates a significant reduction in many instances of diabetes (Ogilvie).

Kidneys. The kidneys in an uncomplicated, untreated case of diabetes are moderately enlarged, pale yellowish pink, and soft. There is cloudy swelling and fatty degeneration of the epithelium of the proximal convoluted tubules, and a conspicuous infiltration with glycogen in the epithelium of Henle's loop (Fig. 19, B, p. 36).

In about 35 per cent of cases of diabetes associated with hypertension, there is a peculiar and characteristic microscopic change in the glomeruli, designated as "intercapillary

the Kupffer cells in the sinusoids of the liver are enormously distended with droplets of fat. In some diabetic patients who are resistant to the physiologic effects of insulin, damage to the liver, either necrosis or cirrhosis, may be observed at autopsy. Insulin acts in part by promoting storage within the liver, and if the liver cell is not capable of storing glycogen, insulin does not have the full physiologic effect (Mirsky, Korenberg, Nelson and Nelson).

Skin. The epidermis in a well treated diabetic patient contains an abundant amount of

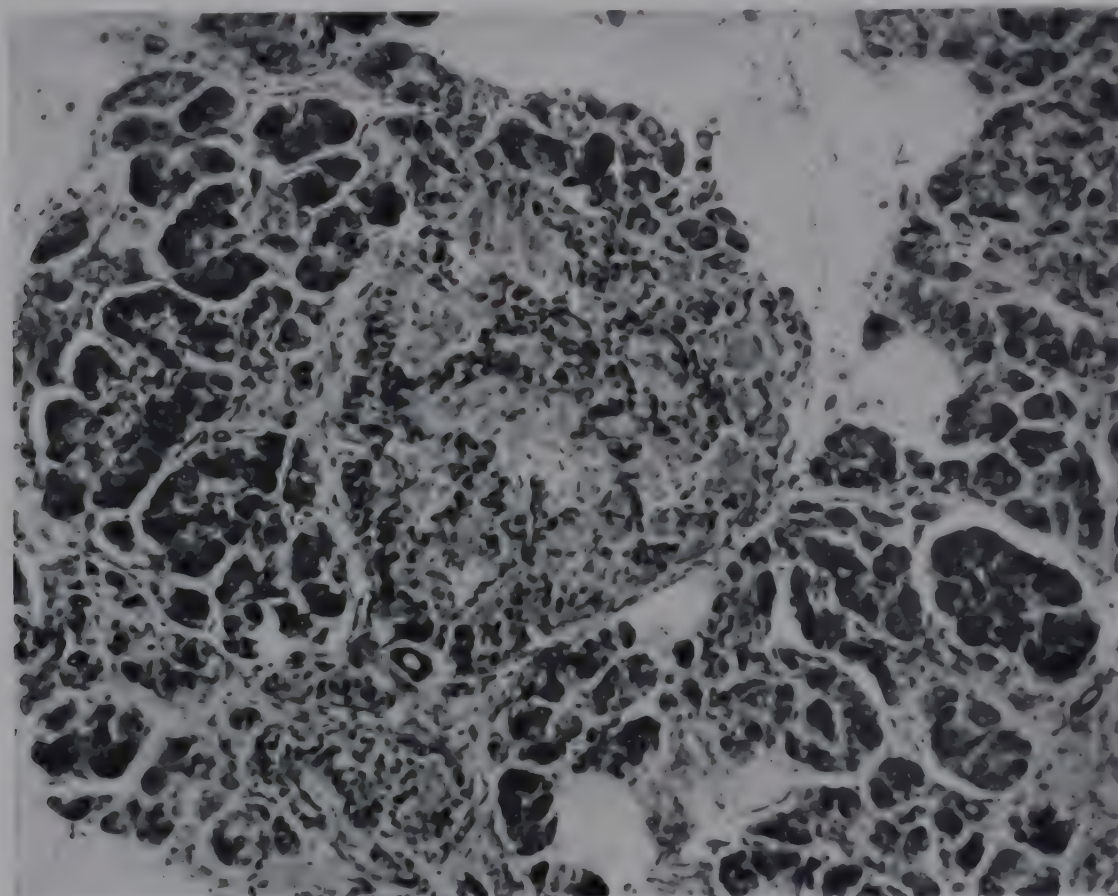


Fig. 420. Hyalinization of an island in diabetes mellitus.

glomerulosclerosis" (Fig. 420). Between the capillary loops a hyaline, acellular material is deposited in the form of lines or round masses. There is no associated inflammation and no thickening of the normal capillary basement membrane (Kimmelstiel and Wilson). This type of glomerular lesion is rarely found in nondiabetic persons, with or without hypertension, and is present more frequently when there is clinical evidence of renal insufficiency with the diabetes (Siegal and Allen; Allen).

Liver. The liver is usually slightly enlarged and yellow. There is a moderate to severe infiltration with fat, and special stains for glycogen reveal little within the cytoplasm but abundant globules in the nucleoli of the hepatic cells. This infiltration of glycogen into nuclei may be observed in many other conditions. In patients who have severe lipemia,

glycogen, which is gradually depleted in the absence of adequate doses of insulin. In many diabetic persons there are small tumors in the subcutaneous tissues, especially in the eyelids, known as "diabetic xanthomas." These result in part from a deposit of cholesterol and other lipid substances in large mononuclear cells, and in other instances represent the accumulation of similar lipids free in the tissues and surrounded by masses of densely collagenous connective tissue. These nodules may on occasion undergo softening and ulceration, and the process is known as "diabetic lipoid necrobiosis."

Spleen. In untreated diabetes with severe lipemia the sinusoids and pulp cords of the spleen are filled with large mononuclear cells, distended with droplets of fat (Fig. 27, B, p. 48).

Eye. Careful study during the last decade has thrown considerable doubt on the assumption that cataracts are commoner in diabetics than in nondiabetics (Waite and Beehan).

Biochemical Findings. Superficially the diabetic person differs physiologically from the normal person in that he is unable to utilize sugar in the usual fashion. More profound study shows that there are two possible defects: (1) a reduced ability to burn sugar in

persons with diabetes in the United States. Diabetes is given as the cause in from 1 to 3 per cent of all deaths. The highest incidence of onset is in the sixth decade, but it may occur at any time during life. The ratio of women to men is 6:4. Diabetes is more common in persons of Jewish and Irish extraction and least common in the Oriental races.

Causal Factors. Of the many causal factors which have been postulated in diabetes, two stand out, heredity and obesity. Less obvious

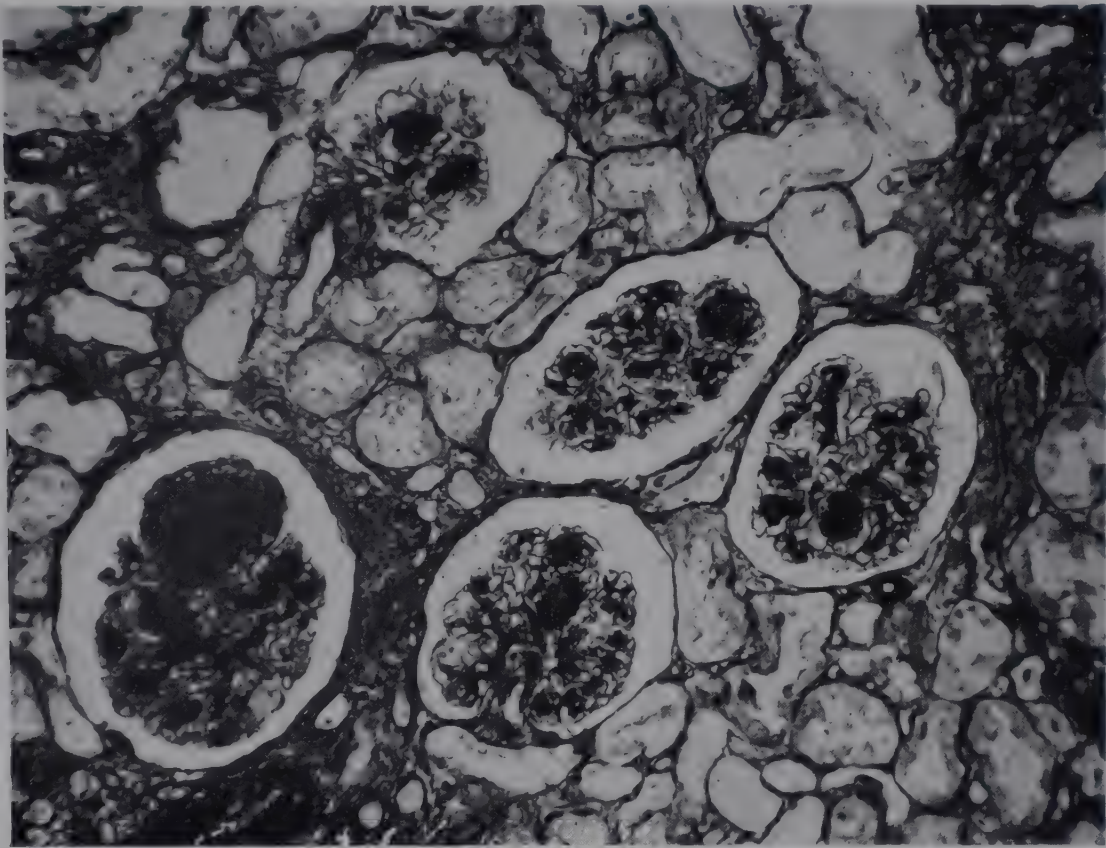


Fig. 421. Intercapillary glomerulosclerosis. (From material reported by Dr. Irving Goodof, Ann. Int. Med.)

the tissues, and (2) overproduction of sugar from protein and fat by the liver.

Majority opinion favors the former defect, but there are certain observations that point to the latter. Factual results or inferential conclusions in support of defective oxidation are: failure of the respiratory quotient to rise when carbohydrate is fed to a diabetic, and the accepted origin of ketone bodies during inadequate oxidation of carbohydrates. Proponents of the overproduction theory answer these statements: A low respiratory quotient is not necessarily an index of failure of oxidation of carbohydrate; ketone bodies are formed in the liver during the interconversion of fat to carbohydrate; and the ability of muscle (from diabetic animals), kept several hours outside the body, to metabolize carbohydrate is normal (Stadie).

Incidence. There are more than 600,000

are endocrine influences, infection, and trauma.

Heredity. Three lines of evidence are available to support the conclusion that diabetes is inherited: (1) its occurrence in twins, (2) its greater incidence in the blood relative of persons with the disease, and (3) agreement of calculated and observed incidence based on the mendelian ratios. The occurrence of diabetes in twins is well shown in Table 52 from White and Pincus.

Diabetes is present in about 7 per cent of the parents and siblings of diabetics, in contrast to 1 per cent of the same relatives of nondiabetics. If it is assumed that a tendency to diabetes is inherited as a mendelian recessive (m) as opposed to the normal dominant (M), White and Pincus have calculated the expected occurrence on the basis of two sets of figures and compared them with the actual

observed incidence. There is remarkable agreement (Table 53).

Obesity. At the time of onset, from 60 to 80 per cent of all adult diabetics are more than 5 per cent above the average weight for their height and age. Diabetic children on the other hand are likely to be taller than the normal. It is perhaps significant that as the average per capita consumption of sugar has

with resistance to infection, such as complement, phagocytes, and humoral antibodies, (3) inadequate function of fixed tissue cells, (4) lowered capacity of tissues to form antibodies, and (5) lowered general nutrition (Marble, White, and Fernald; Richardson). The more common infections are carbuncles of the skin (Williams) and pyelonephritis (Harrison and Bailey).

TABLE 52. INCIDENCE OF DIABETES IN THE SIBLINGS OF NONDIABETIC, DIABETIC, DISSIMILAR, AND SIMILAR TWINS AND OF DIABETES IN THEIR PARENTS

Types of Population	Number of Siblings	Percentage Having Diabetes	Percentage of Parents Having Diabetes
Control.....	862	0.6	2
Diabetic.....	2835	5.0	9
Dissimilar.....	29	7.0	10
Similar.....	19	63.0	5

increased in the last sixty years, there has been a corresponding increase in the morbidity from diabetes.

Endocrine Glands. The known effect of pituitary, thyroid, and adrenal glands on carbohydrate metabolism, and the occurrence of diabetes, glycosuria, and hyperglycemia in some disease of these endocrines, have suggested a possible relation. With present knowledge little more can be said.

Trauma. Despite many claims to the contrary, no indisputable proof that diabetes is causally related to trauma has been submitted. Further study of the effects of trauma on a potential diabetic (one with a hereditary background) is needed (Joslin).

Clinicopathologic Correlation. Before the discovery of insulin, the average duration of life after the onset of diabetes was five to six years. Today it is over twelve years, and the

TABLE 53. EXPECTED AND ACTUAL DIABETIC SIBLINGS OF 175 UNIDENTIFIED GENETICALLY DIABETIC PARENTS

Type of Cross	Expected Siblings by Joslin's Data	Expected Siblings by Massachusetts Data	Observed
Mm x Mm.....	121	90	98
Mm x mm.....	63	39	48
mm x mm.....	13	8	8

Hyperglycemia. The fact that continued hyperglycemia in dogs will result in degranulation of the beta cells suggests that poor control of the diabetes in man may induce a vicious cycle of increasing severity (Barron and State).

Infection. There is little evidence that diabetes is caused by infection, but abundant observation that infections are unusually severe and extensive in diabetics. The following have been offered as possible causes: (1) increased sugar content of blood and tissues (Menkin), (2) decreased activity of elements associated

child diabetic has an equal chance with the adult diabetic.

Relation to Arteriosclerosis. Early in the study of diabetes it was noted that arteriosclerosis was unusually common in more severe cases of diabetes, but since the diabetic lives and dies at an age when arteriosclerosis has the highest incidence, some recent investigators have questioned the cause and effect relation. There is good evidence that coronary arteriosclerosis is far commoner as a cause of death in diabetics (60 per cent of all deaths from arteriosclerosis) than in non-

diabetics (Clawson and Bell), but the higher incidence of arteriosclerosis and gangrene of the extremities has been challenged (Lisa, Magiday, and Hart). Much more careful investigation is needed. The high incidence of vascular disease in young diabetics is support for a positive relation (Root and Warren).

Relation to Other Conditions. As compared to the general population, persons with diabetes develop cancer of the pancreas twice as frequently, suffer from a more severe and progressive form of tuberculosis (Wiener and Kavee), and have gallstones about twice as often. The maternal and neonatal death rates in pregnant women with diabetes are higher (White and Hunt). Newborn infants of diabetic mothers in some instances are larger (White, Titus, Joslin, and Hunt), and may show symptoms of hyperinsulinism in association with hypertrophy of the islands of Langerhans (Helwig).

Causes of Death. In the extensive experience of Joslin, disease of the cardiovascular-renal organs accounts for about 60 per cent of deaths, infections for 15 per cent, cancer for 8 per cent, tuberculosis for 4 per cent, diabetes alone for 4 per cent, and all other causes for 9 per cent.

Experimental Diabetes. In animals, removal of over seven-eighths of the pancreas will result in diabetes. It has also been shown that injection of alloxan will cause selective necrosis of the islands and diabetes (Bailey and Bailey). Injection of certain extracts of the pituitary (diabetogenic hormone) induces diabetes (Ham and Haist).

Effects of Parenteral Insulin. In a few patients foci of atrophy of the subcutaneous tissue develop at the site of injection of insulin (Wirtschafter). Rarely, a sensitivity to insulin is observed (Goldner and Ricketts).

Lipocaic Deficiency

Fisher, and Allan, Bowie, Macleod, and Robinson, demonstrated that after a period of several months depancreatized dogs developed extensive fatty metamorphosis of the liver and died. The addition of raw pancreas was found to prevent the condition, and Best and Huntsman believed that the effect of the raw pancreas resulted from its content of choline. However, Dragstedt, Van Prohaska, and Harms demonstrated that there was some

other substance in the pancreas which prevented the condition, and they proposed the term "lipocaic" for this unknown substance.

These experimental studies have led to the establishment of a condition in man which has been called the "pancreaticohepatic syndrome." In certain conditions of the pancreas in which there is extensive destruction, there is an associated fatty metamorphosis of the liver. In some of the cases of atrophy and fibrosis of the pancreas in children associated with chronic respiratory infection, there is a moderate to advanced fatty metamorphosis of the liver.

Not all cases of fatty metamorphosis of the liver associated with diabetes are the result of lipocaic deficiency. It can be the result of inadequate treatment with insulin. In patients and in dogs in whom a lipocaic deficiency has been established, there is hypersusceptibility to insulin. Thus a completely depancreatized dog with lipocaic deficiency and fatty metamorphosis of the liver may require only two or three units of insulin per day, and larger amounts may provoke hypoglycemic shock (Dragstedt).

Tumors of the Islands of Langerhans

Although tumors of the islands of Langerhans had been known for many years, Wilder, Allan, Power, and Robertson first demonstrated their association with hyperinsulinism. Some tumors secrete large amounts of insulin, and others are apparently physiologically inactive. Histologically, there is no difference between the two, which may be either benign or malignant. In general, there are symptoms of hypoglycemia in about 20 per cent of all anatomically demonstrable tumors of the islands. Similar neoplasms have been reported in animals (Slye and Wells).

Pathologic Anatomy. The tumors are pinkish gray, discrete, and usually sharply encapsulated. They are multiple in about 12 per cent of instances, and are commoner in the tail than in the body and head of the pancreas. On section the tumors are seen to be composed of a gray, finely granular, soft tissue, separated into small and large islands by narrow or broad connective-tissue trabeculae. Foci of calcification are common. There is a definite fibrous capsule about the tumor. The cells resemble the cells of the normal island.

They are usually arranged as short anastomosing cords, separated from one another by thin-walled capillaries. The nuclei in general are relatively large, and giant cells may be present (O'Leary and Womack). By special staining methods the alpha and beta cells can be demonstrated (Gomori). Most physiologically active tumors are composed of beta cells admixed with only a few alpha cells (Womack, Gnagi, and Graham).

Malignant Tumors of the Islands of Langerhans. In addition to the usual adenoma, clearly benign on both clinical and histologic grounds,

pancreas is usually essentially normal. There may be some hypertrophy of the islands. In the pituitary gland there are variable but not significant changes, from hypertrophy of the eosinophils to basophilic invasion of the posterior lobe.

Incidence and Causal Factors. Tumors have been reported at all ages, but symptoms of hypoglycemia are commoner in the young. The sexual preponderance is 5:4 in favor of men.

Assay of Hormones. An excessive amount of insulin may be demonstrated in the neo-



Fig. 422. Tumor of islands of Langerhans. From a patient with typical symptoms of hypoglycemia cured by surgical removal of the tumor.

there are two types of malignant tumors of the islands. In one the diagnosis is based on invasion of the capsule, and in the other on the presence of metastases. With the former there may be some questions concerning the true potentialities of the neoplastic cells (Frantz).

Histogenesis. The islands of Langerhans are normally derived from multiplication of the cells of the interrelated ducts. In the islet cell tumors there is considerable histologic evidence that the cell is derived from the smaller intercalated ducts. At times a direct continuity between a small duct and a neoplastic cell may be demonstrated (O'Leary and Womack). Similar tumors arising in aberrant pancreas have been reported (Ballinger).

Secondary Changes. The remainder of the

plastic tissue by proper methods of extraction and assay.

Clinicopathologic Correlation. The tumors are rarely large enough to be palpable, and the symptoms result entirely from hypoglycemia. Most of these are centered in the nervous system, and are extremely bizarre and inconstant. There is first mental retardation, lassitude, and mild mental confusion, followed by increasing pallor, profuse perspiration, restlessness, confusion, and finally stupor or coma, with or without convulsions. The administration of a small amount of sugar results in prompt recovery (Duff).

Pathologic Effects of Hyperinsulinism. In addition to the hypoglycemia and hyperinsulinism associated with tumors of the islets,

a similar clinical condition is observed under a number of other circumstances. Occasionally, an overdose of insulin may be given to a patient with diabetes, or the hypoglycemia associated with disease of the liver may become significant. Finally, a recognized form of treatment for schizophrenia is the induction of convulsions with an overdose of insulin. The pathologic changes in all of these conditions are similar: petechiae throughout all parts of the brain, chromatolysis of the ganglion cells, pyknosis of the nuclei, and degeneration of the cytoplasm. There is no cellular infiltration (Moersch and Kernohan).

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XCIX

Diseases of the Parathyroid Glands

The four parathyroid glands, arranged as an upper and lower pair about the superior and inferior poles of the thyroid, are each 6 to 10 by 3 to 6 by 2 to 4 mm. in size, and average 40 to 80 mg. in weight. They are yellowish red or brownish red and soft, inelastic, and richly vascularized. Four types of parenchymal cells are recognized: chief cells, clear cells, light oxyphilic, and dark oxyphilic cells. With increasing age there is fat infiltration of the glands and increase in the relative number of oxyphilic cells.

Physiologic Activity. The parathyroids elaborate and secrete into the blood a hormone—parathormone—which rapidly mobilizes calcium and maintains the serum calcium at a normal level (see Chapter VI) (Albright).

Hyperplasia of the Parathyroids. The parathyroid glands increase in size in response to decrease in ionized serum calcium: rickets (Erdheim), osteomalacia, defective intestinal absorption of calcium, and certain forms of renal insufficiency (Pappenheimer).

Diseases of the Parathyroids. There are two distinctive diseases primary in the parathyroid glands, tetany, related to hypofunction, and osteitis fibrosa cystica, related to hyperfunction.

Tetany

Tetany is a clinical syndrome characterized by increased muscle and nerve irritability and tonic spasms.

Types. Tetany may occur in any condition associated with a fall in the total serum calcium to 7 mg. or less per 100 cc. and of the ionized calcium to from 1.2 to 2 mg. per 100 cc. The general causes are hypofunction of the parathyroid, alkalosis, and interference with absorption and ionization of calcium, in

turn related to dietary deficiency, excessive serum phosphorus, or a deficiency of vitamin D.

Pathologic Anatomy. Pathologic changes in the parathyroids are not consistent. Hemorrhage, cysts, atrophy, and inflammation have been described in the idiopathic type. If the condition persists and there is a reduction in the serum calcium, the parathyroids undergo hypertrophy.

Clinicopathologic Correlation. The principal signs and symptoms are the result of neuromuscular hyperexcitability—symmetrical, painful muscular spasm, most conspicuous as carpopedal spasm.

Hyperparathyroidism—Osteitis Fibrosa Cystica; Adenoma of the Parathyroid Glands

Our present knowledge of osteitis fibrosa cystica, or von Recklinghausen's disease of bone, is based on three significant investigations: first, the original description of the pathologic changes in the bones by von Recklinghausen in 1891; second, the conclusive demonstration of a relation of the parathyroids to disease of the bone by Erdheim in 1907; and third, the successful cure of a patient by removal of a tumor of the parathyroid by Mandl in 1926. Between the second and the third should be included the experimental production of tetany by removal of the parathyroid by MacCallum and Voegtlin in 1909, and the isolation of parathormone by Collip in 1925.

Pathologic Anatomy. Changes in Bone. Changes are most prominent in the diaphysis of the long tubular bones. The bone is focally expanded and the cortex thin. The medullary cavity contains only a few narrow trabeculae, and the marrow is partly replaced by grayish

white, firm foci, set through with single and multiple cysts. There are regions of recent and old hemorrhage. The haversian canals are widened and filled with a loose fibrous tissue. Osteoclasts are numerous. In larger fibrous foci, immature lamellar bone may form. Giant

glands may contain an adenoma. In diffuse hyperplasia the clear cell is the dominant cell, but in adenomas the chief cell type predominates. The size of the adenoma varies from a few millimeters to many centimeters, and is in direct proportion to the severity of the dis-



Fig. 423. Osteitis fibrosa cystica. (Armed Forces Institute of Pathology, Neg. No. 70860.)

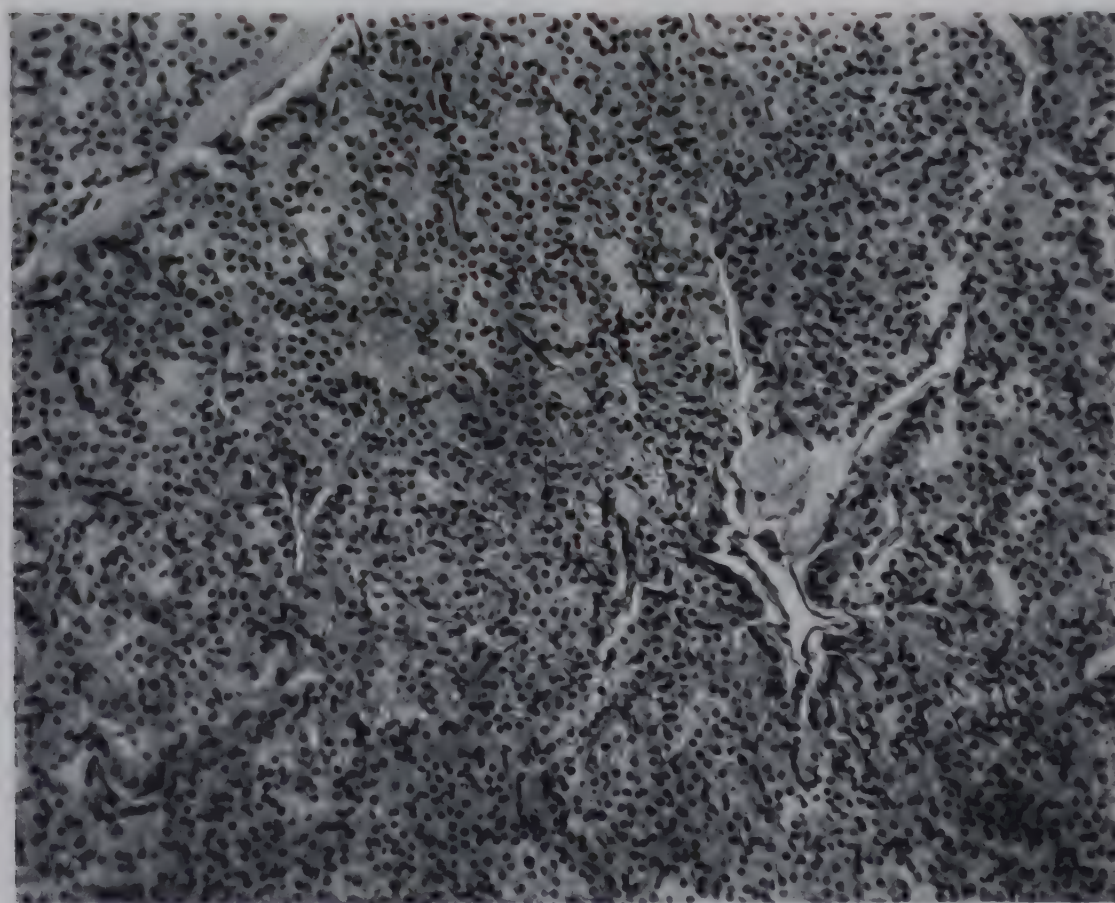


Fig. 424. Adenoma of parathyroid gland from a patient with hyperparathyroidism. (Slide by courtesy of Dr. Paul Wheeler.)

cells are numerous, especially about foci of old hemorrhage, and the entire region may have the appearance of giant cell tumors. The cysts are lined by dense connective tissue and filled with a protein-poor fluid (Jaffe).

Changes in the Parathyroids. The parathyroids may be diffusely enlarged, or one or two

ease. The cells of the adenoma are arranged in cords and sheets, supported on a delicate connective-tissue stroma. In hyperplasia the giant-sized clear cells with basal nuclei are in acinic form (Castleman and Mallory). Some tumors are malignant (Meyer and Ragins).

Changes in the Kidneys. In about one-half

of cases there are renal calculi composed of calcium phosphate. In some of these there are no changes in the bone, and the renal calculi are the only evidence of hyperparathyroidism. Secondary pyelonephritis is common, and a significant number of patients die of renal failure (Albright, Baird, Cope, and Bloomberg). In addition to the calculi there may be metastatic calcification in the kidneys, stomach, and lung.

Pathogenesis. The order of events appears to be excessive activity of the parathyroid, extraction of minerals from the soft tissues and excretion of them, mobilization and withdrawal of minerals from the bones (not only calcium but also the earthy alkaline substances to compensate for the acidosis), proliferation of osteoclasts to phagocytize the decalcified matrix, and proliferation of fibrous tissue to replace the bone (Jaffe). To account for the low serum potassium some suggest that the initial lesion is a lowering of the renal threshold for phosphorus by the action of parathormone (Albright and Ellsworth).

Clinicopathologic Correlation. Osteitis fibrosa cystica is a disease of persons between thirty and fifty years of both sexes. The serum calcium is increased and the serum phosphorus decreased. There is a marked negative calcium balance, with 70 to 90 per cent of the total excretion of calcium by the kidneys. The serum phosphatase is slightly increased.

Focal lesions both in the bones and in the kidneys are readily identified on a radiogram. The thinness of bone is responsible for the frequent spontaneous fractures. Pain is probably caused by minute trabecular fractures. The disturbance in calcium metabolism is responsible for tetany, diminished irritability of muscle and nerve leading to muscular weakness and hypotonia. The excessive excretion of calcium and phosphorus requires large quantities of fluid, and the patient therefore has polydipsia and polyuria. The nausea and vomiting are probably expressions of periodic acute hyperthyroidism. In late stages there may be gross deformity of the skeleton and reduction in height.

Renal Rickets. Occasionally, a child or an adult with chronic renal insufficiency and longstanding acidosis develops a lesion of bone similar to osteitis fibrosa (Ginzler and Jaffe). There may be significant enlargement of the

parathyroids as the result of hyperplasia of chief cells. This is in contrast with the clear cell hyperplasia of primary hyperthyroidism (Castleman and Mallory).

Progressive Atrophy of Bone. This condition, somewhat similar to osteitis fibrosa, has been described in both animals and man with and without disease of the parathyroids. The trabeculae are dissected apart by a loose fibrous tissue, and osteoclasts are conspicuous. There is little new formation of bone.

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C

Diseases of the Thymus and the Pineal Body

The thymus and the pineal body were originally grouped by anatomists and physiologists with the endocrine glands. Modern investigation has failed to justify this classification, and in man and animals results of removal and of injection of extracts have been equivocal.

The Thymus

The thymus develops as a bilateral organ from the endoderm of the third and fourth gill arches, in association with the parathyroid glands. There is a gradual migration caudally until at birth it occupies a position in the superior mediastinum, and the originally paired lobes fuse to form a single midline organ. Until the second fetal month the anlage is distinctly epithelial in structure, but at this time the cells become more loosely arranged and develop protoplasmic processes to form a reticulum. Somewhat later, lymphocytes appear, the origin of which is in doubt. Some maintain that they are modified reticulum cells, and others that they are derivatives of mesenchyme, which wander into the developing thymus.

The Normal Thymus. The normal weight of no other organ in the body has excited so much controversy and been the subject of so exhaustive an investigation as that of the thymus. In the case of other organs the weights at different ages and the velocity of growth and involution have been well established, but with the thymus secondary concepts have served to confuse the picture. The real question is, What is a *normal* thymus? Investigators are arrayed in two schools: first, those who contend that the large thymus found in cases of sudden unexpected death in children represents enlargement which is a part of a general constitution predisposed to sudden death from 'trivial causes'; and secondly, those who contend that this large thymus is not en-

larged but the true normal thymus, unaffected by general or local disease. According to the latter idea the thymus and lymphoid tissue are labile and undergo prompt and marked involution within a few days of the onset of most acute and chronic diseases. If the weights of the thymuses in those who die of accidental causes are tabulated statistically, certain general conclusions are evident. There is a gradual growth during fetal life, a temporary loss in weight after birth, followed by recovery and continued growth until puberty, at first rapidly and then more slowly, and finally a slow, at times irregular involution throughout the remainder of life (Boyd). The thymus doubles the birth weight in about two years, and trebles it by eleven years. For the period of fetal growth Scammon has calculated the regression formula as follows:

$$TW = 0.0036418 BW - 0.474$$

when *TW* is the weight of the thymus and *BW* is body weight.

Involution of Inanition and Disease. If one is to accept the concept of the normal thymus which has been presented in the preceding paragraph, it follows that the small, firm thymus found in most autopsies is pathologic. Proof for this is given in the data collected by Boyd for the weight of the thymus in relation to the duration of the illness (Table 54).

This involution is characterized by the emigration of lymphocytes from the cortex. The interstitial tissue and lymphoid vessels are filled with lymphocytes. The few leukocytes normally found in the trabeculae disappear. The medulla becomes richer in lymphocytes, so that the distinction between the two parts is obscured. Mitoses are inconspicuous, and the reticulum cells of the cortex are swollen and filled with globules of fat. Hassall's corpuscles appear to be increased because of the shrinkage of the organ, but actually there is

an absolute decrease. The same changes occur after irradiation, but in addition there is extensive phagocytosis of lymphocytes by the reticulum cells (Hammar).

Status Thymicolymphaticus. For more than three hundred years cases of sudden death without adequate cause, when viewed by the usual pathologic standards, have been observed. Almost without exception the large thymus has attracted the attention of the prosector, and both a scientific and a fictional literature have grown up about these cases, variously termed "laryngismus," "asthma thymicum," "stridor thymicus," "mors thymica," "status lymphaticus," "status thymicolymphaticus," and "status hypoplasticus."

It seems possible that this syndrome depends on an inadequacy of some function of the adrenals, sex glands, and autonomic nervous system, which is associated with lowered resistance or increased susceptibility to a great variety of nonspecific physical and chemical agents (Marine).

Young and Turnbull, however, after an exhaustive investigation, deny that any condition similar to status thymicolymphaticus exists as a pathologic entity. Clearly it is impossible at the present time to present any definite conclusions, and an open mind must be maintained.

Tumors of the Thymus. It is probable that with the exception of involvement of the thymus in malignant lymphoblastoma and by varied mesodermal tumors, there is only one distinctive tumor of the thymus—thymoma.

Pathologic Anatomy. The region of the thymus is replaced by a soft, white tumor mass which may be encapsulated or infiltrative. Microscopically the essential cell is large with a pale nucleus and a reticulated cytoplasm devoid of definite cell walls. The cells are arranged in alveoli or cords separated by delicate trabeculae. In many tumors there is focal whorling of the cells into structures similar to Hassall's corpuscles. Throughout most tumors are lymphocytes, either focally or diffusely. Malignancy is manifest by local invasion of the thoracic structures or wall or by distant metastases (Anderson and Conrick).

Clinicopathologic Correlation. The signs and symptoms are largely the result of compression of the trachea, and of nerves and blood vessels. An endocrine activity has not been demonstrated,

TABLE 54. WEIGHT OF THYMUS IN RELATION TO LENGTH OF ILLNESS

Nature of Cases	Ill Less than 24 Hours				Ill 1 to 7 Days				Ill 1 Week or More			
	No. Cases	Percentage			No. Cases	Percentage			No. Cases	Percentage		
		Above*	Within*	Below*		Above*	Within*	Below*		Above*	Within*	Below
Theoretical expectancy.	..	25	50	25	..	25	50	25	..	25	50	25
Accidents.....	95	58	35	58	16	0	25	75
Undetermined causes...	157	27	54	19	47	66	32	66	30	3	17	80
Infections.....	53	21	47	32	195	69	25	69	488	1	5	94
Congenital defects.....	21	19	43	38	25	64	32	64	32	0	6	94
Miscellaneous causes...	38	32	47	21	54	56	37	56	203	4	22	73
Total.....	269	25	48	27	416	64	30	64	769	2	11	87

* The designations "above," "within," and "below" indicate the percentages in which the weight of the thymus was within the interquartile ranges of the normal graphic standard.

Relation to Myasthenia Gravis. About 10 per cent of patients with myasthenia gravis have a tumor of the thymus. This type of myasthenia is more common in men between forty and sixty years of age and follows a more rapid course. The tumor is benign and of the usual type (Castleman and Norris).

The Pineal Body

Aside from tumors (discussed in the chapter on tumors of the central nervous system,

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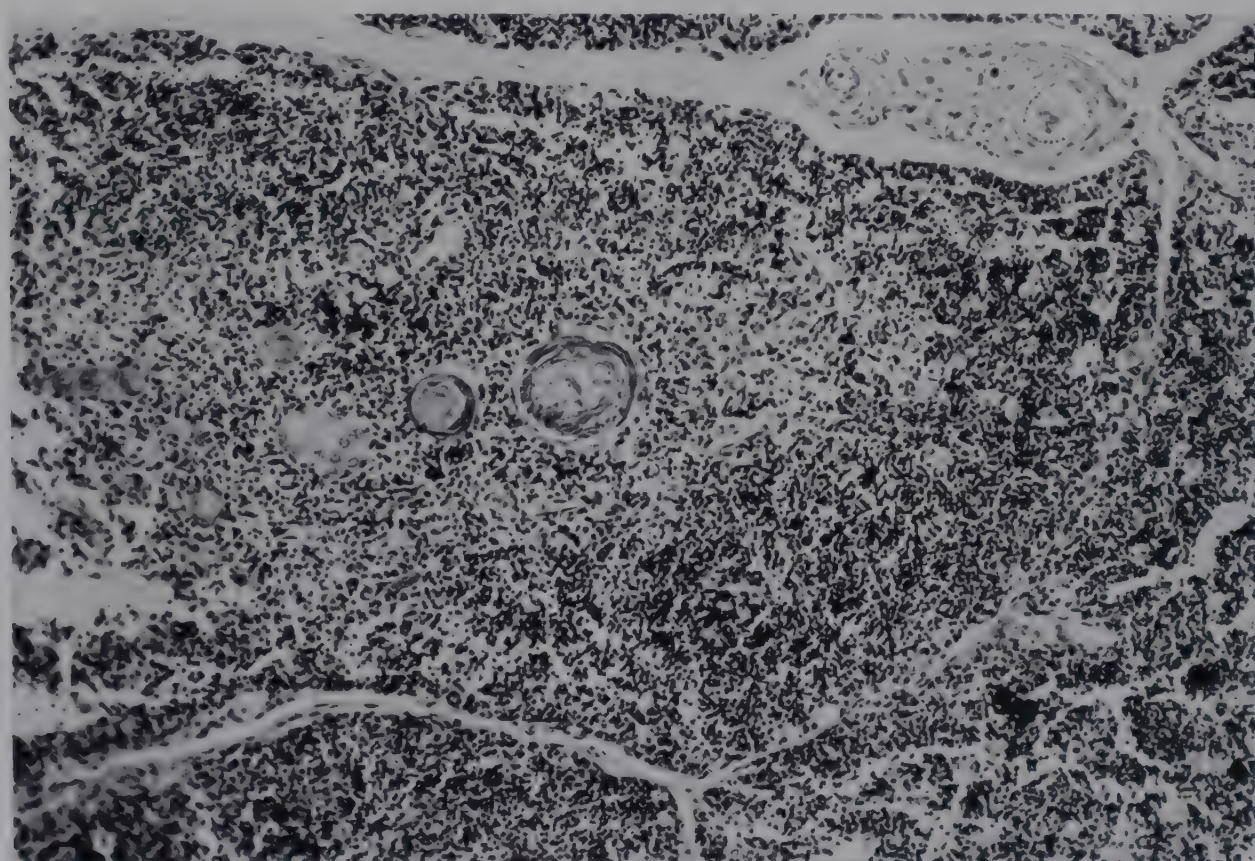


Fig. 425. Involution of thymus in association with an acute infectious disease.

p. 951), there are few important lesions of the pineal. Shortly after birth, calcification begins in the habenular commissure and extends to the pineal. By the time of puberty all pineals contain foci of calcification, and in a few it is visible on a radiograph as a landmark for localization of the midline.

The relation of disease of the pineal to precocious puberty and the effect of extracts on animals is controversial. The best evidence today is that the pineal is not an endocrine gland, and has no influence on sexual, somatic, or mental development. The syndrome in association with tumors of the pineal occurs with all types of tumors, and hence would appear to be the result of irritation or pressure on the surrounding nerve centers (Russell and Sachs; Martin and Davis).

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CI

The Ovary—The Testis—The Gonads as Endocrine Glands

Sex connotes a definite and sharp separation of maleness and femaleness. This separation is made up of innumerable small differences, which, taken singly, are relative. Yet on the most careful scrutiny it is found that no one person represents the complete development of one sex, but is a mixture of some maleness and some femaleness, with a preponderance of one or the other.

dites and male pseudohermaphrodites. In the *male pseudohermaphrodite*, there is a testis on each side, but the internal genitalia of both sexes are retained; that is, there is a prostate, seminal vesicle, vas deferens, vagina, uterus, and uterine tubes. The vagina usually empties into the urethra at the verumontanum. The penis is small and frequently hypospadiac. The scrotum is poorly developed, and the testes are



Fig. 426. Hypertrophy of clitoris in a pseudohermaphroditic newborn infant.

Intersexuality—Hermaphroditism

According to Greek mythology, the child of Hermes and Aphrodite, who was remarkably endowed with the attributes of both the father and the mother, was given the name of both parents, "Hermaphrodita." This term has been used in medicine since that day to designate an individual in whom the secondary sexual characteristics are underdeveloped or malformed, and inconsistent with the sex of the gonad.

Types of Pseudohermaphroditism. The simplest classification of pseudohermaphroditism is the use of a single adjective to designate the sex of the gonad: female pseudohermaphro-

rarely fully descended, remaining either in the canal or in the abdomen. In the *female pseudohermaphrodite*, there is an ovary on each side, usually in the normal position, but small and frequently cystic. The vagina is rudimentary and opens into the urethra, thus forming a persistent urogenital sinus. Above the opening of the vagina, in the wall of the urethra, there is a definite prostate. The clitoris is hypertrophic. In many instances there is hypertrophy of the adrenal glands (Young).

True Hermaphroditism. In this condition there is a testis on one side and an ovary on the other side (gynandromorphism) or an ovotestis on one or both sides. Most hermaphrodites menstruate. The phallus is usually

large and hypospadiac. The vagina may open normally on the perineum or into the urethra. The uterus is infantile, and there is a definite prostate about the urethra.

Hypospadias and Epispadias. In about one out of every 250 persons, the penile portion of the urethra formed as a groove does not close, so that the external orifice is on the undersurface of the base of the penis—hypospadias. Epispadias is a far more complicated and rare condition, in which the urethra exists as a groove on the upper surface of the penis and the urethra opens onto the lower abdominal

lar, with prominent cheekbones. The eyes are small and deeply set. The nose is short and thin. The skin is pale and delicate, and the hair on the face and body is of the lanugo type. The external genitalia are small. The prostate and seminal vesicles are small and fibrotic (Tandler and Grosz).

Female Sex. In the female sex congenital aplasia of the ovaries is associated with a definite complex frequently referred to as Turner's syndrome. There are severe sexual infantilism, primary amenorrhea, dwarfism, webbing of the neck, and cubitus valgus. The urinary ex-

TABLE 55. INCIDENCE AND PROGNOSIS OF OVARIAN TUMORS

Type	Per Cent of All Tumors		Per Cent with 5-Year Survival of Malignant
	Benign	Malignant	
Serous cystadenoma	19.9	9.2	35.7
Pseudomucinous cystadenoma	20.8	3.1	47.1
Unclassified cystadenoma	2.1	—	—
Dermoid cyst	18.0	0.2	0.0
Granulosa cell tumor, etc.	1.4	0.6	0.0
Fibroma	20.6	—	—
Brenner tumor	1.1	—	—
Undifferentiated carcinoma	—	1.4	18.2
Hypernephroma	—	0.3	25.0
Dysgerminoma	—	0.1	0.0
Miscellaneous	0.8	0.4	60.0

wall. There is always a failure of union of the pubic bones and occasionally an exstrophy of the bladder (Young).

Eunuchism and Eunuchoidism

A person from whom the gonads have been removed is known as a "eunuch." A person still possessing a remnant of the gonad, but showing all of the characteristics of eunuchism, is known as a "eunuchoid."

Male Sex. The physical and anatomic characters of a eunuch depend upon the time of castration. If the gonadectomy or disease of the gonad takes place before puberty and the closure of the epiphyses, the typical tall person with long extremities usually results, although a smaller percentage develop the adipose type of eunuchism. If the gonadectomy is performed after puberty, there can be no material change in the physical conformation of the body, and alterations will be restricted to the secondary sexual organs. The face of the eunuch is angu-

cretion of FSH is increased (Lisser, Curtis, Escamillo, and Goldberg).

The Ovary

CLASSIFICATION OF CYSTS AND TUMORS OF THE OVARY

No classification of tumors of the ovary is entirely satisfactory because there is inadequate knowledge of the histogenesis and cause of these tumors. The following simple classification is based on morphology, and incorporates as much clinical and endocrinologic information as is proved.

- I. Retention cysts
 - 1. Follicular
 - 2. Luteal
 - 3. Atretic
- II. Cystadenoma
 - 1. Serous
 - 2. Pseudomucinous
- III. Endometriosis and endometrioma
- IV. Solid intrinsic tumors derived from gonadal epithelium of either sex

1. Functional with excessive estrogen
 - (a) Granulosa cell tumor
 - (b) Theca cell tumor
 - (c) Lutein cell tumor
2. Functional with excessive androgen
 - (a) Arrhenoblastoma
3. Nonfunctional
 - (a) Dysgerminoma
 - (b) Unclassified carcinoma
- V. Tumors derived from mesenchymal elements—fibroma, myoma, angioma, etc.
- VI. Tumors apparently derived from fetal inclusions from other organs
 1. Brenner tumor
 2. Mesonephroma of ovary
 3. Adrenal cell tumor
- VII. Teratoma and dermoid cyst

the evidence indicates that retention cysts of the ovary are directly related to hyperactivity of gonadotropins, as exemplified in the occurrence of cysts with hydatidiform mole and chorio-epithelioma (Novak and Koff); in acromegaly; and in newborn infants. The fluid within the cysts in general contains appreciable amounts of estrogen (Adair and Watts).

Clinicopathologic Correlation. Most women with multiple retention cysts of the ovaries have no complaints, but there are two definite clinical syndromes associated with the hyperestrinism: cystic hyperplasia of the endometrium with uterine bleeding; and hyperemia of

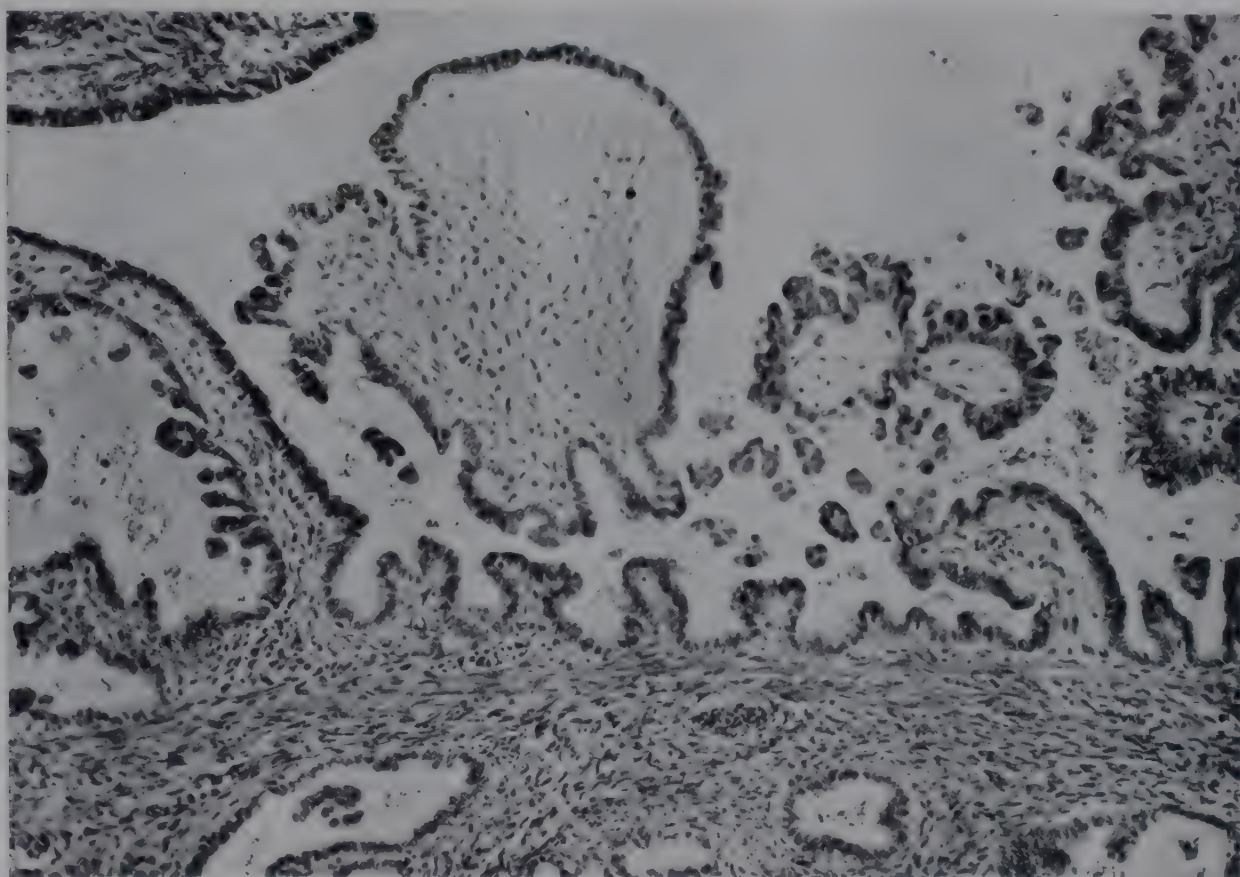


Fig. 427. Serous cystadenocarcinoma of the ovary. (Slide by courtesy of Dr. John Hobbs.)

Incidence and Prognosis. The accompanying table taken from the study of 1740 tumors of the ovary by Allan and Hertig gives the relative incidence and prognosis of most of the preceding types.

RETENTION CYSTS OF THE OVARY

Pathologic Anatomy. In many ovaries there are small cysts, 2 to 5 mm. in diameter, lined with granulosa and theca cells. A few cysts have a thick wall composed of theca cells, partially or completely luteinized. The content of the cyst is for the most part a clear limpid fluid, but occasionally there is fresh or old blood pigment dissolved or suspended in the fluid.

Causal Factors and Hormonal Activity. All

the genitalia, tenderness of the breasts, and amenorrhea. Rarely, a cyst of the ovary lined by granulosa cells produces precocious puberty in girls (Mengert). The luteal cysts are more likely to contain blood, and they occasionally rupture into the peritoneal cavity and give alarming symptoms of hemoperitoneum (Harris and Groper).

Cystic Ovaries in Infants. About 25 per cent of all newborn infants have multiple small cysts in both ovaries (Gerlach), and it has been assumed that these cysts are the result of hormonal stimulation from the mother.

Cysts of Broad Ligament. The cysts commonly designated as para-ovarian cysts originate from three structures: mesonephric duct, mesonephric tubules, and paramesonephric

(müllerian) duct. The epithelial type in each is distinctive (Gardner, Greene, and Peckham). The cyst may be interligamentous or pedunculated. Cysts in this region designated as Walthard bodies originate from invaginations of the peritoneum (Greene, Peckham, and Gardner).

CYSTADENOMA OF THE OVARY

Pathologic Anatomy. The cystadenoma of the ovary differs from the retention cyst in that it is lined by a single layer of cuboidal or columnar cells which bear no resemblance to the normal graafian follicle. It is usually a single

Incidence. Cystadenoma is commonest during adult sexual life, from twenty to forty years of age.

Hormonal Activity. Rarely in cystadenomas there is an appreciable amount of biologically active estrogen in the cystic fluid, thus supporting the idea that they are derived from the cells of the graafian follicle (Watts and Adair).

Clinicopathologic Correlation. The principal sign in cystadenoma of the ovary is the presence of a tumor mass in the pelvis, giving rise to a feeling of heaviness and fullness in the lower abdomen. There may be dysmenorrhea

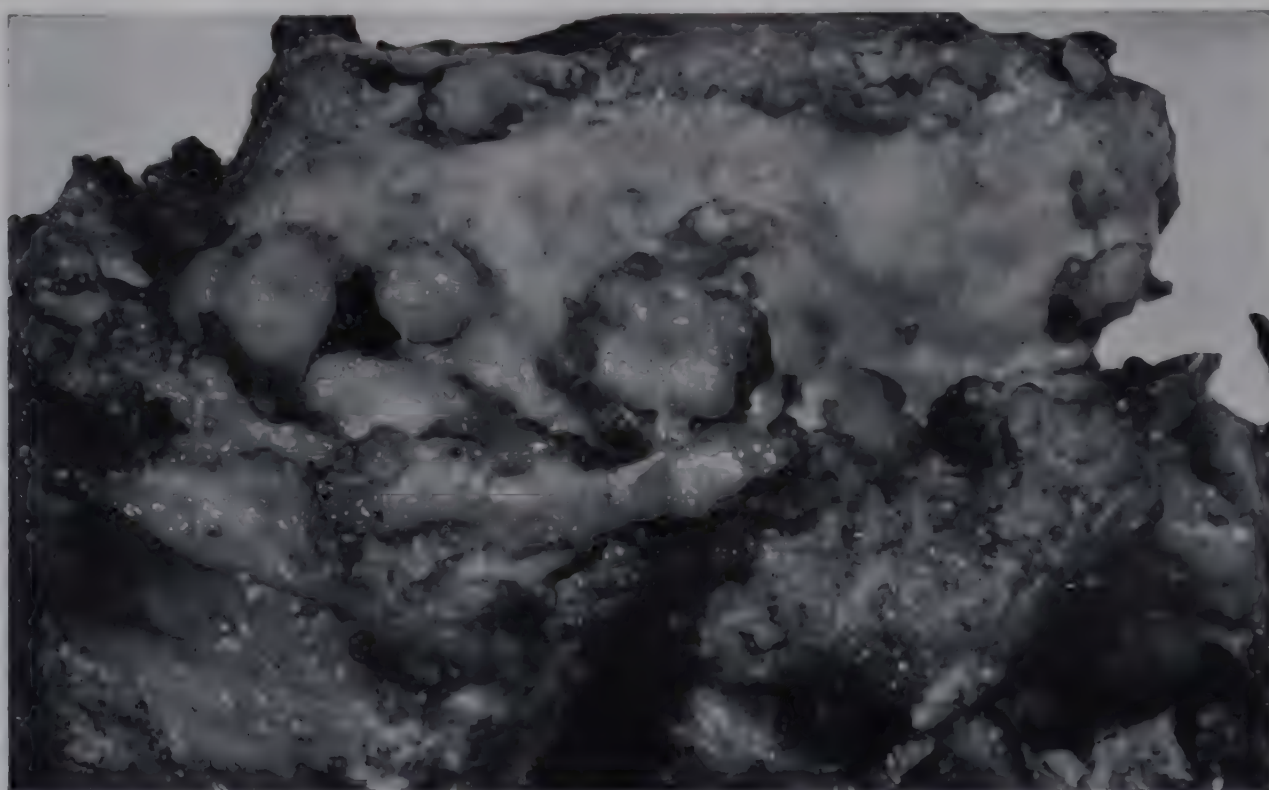


Fig. 428. Pseudomyxoma peritonei. (Photograph by courtesy of Dr. Lauren Ackerman.)

large cyst into which numerous papillae project. Two types are recognized: the serous and the pseudomucinous. In the *serous cystadenoma* the cavities are filled with a clear, limpid fluid, and the epithelial lining is a single layer of cuboidal cells. In the *pseudomucinous* variety the liquid is thick and viscid, and the epithelium is of the tall columnar type. Within the epithelial cells there are globules of mucus (Reagan). From 10 to 20 per cent are malignant, and are designated as "cystadenocarcinomas."

Histogenesis. The exact origin of the cystadenoma is not known. At least seven structures or tissues have been suggested: germinal epithelium of the ovaries, follicular epithelium, remnants of the wolffian system, one-sided development of a teratoma, and inclusion of tubal, endometrial, or cervical glands in the ovaries (Schiller; MacLeod).

because of the destruction of ovarian tissue. Pressure of the tumor mass on the ureter leads to hydronephrosis. In those cysts which are attached to the ovary or broad ligament by a pedicle, rotation or twisting of the pedicle produces occlusion of the blood vessels and infarction of the cyst with characteristic symptoms. Twisting of the pedicle is commoner in young children and during pregnancy.

Implantation Metastases. Pseudomyxoma Peritonei. In addition to metastases by way of the blood stream and lymphatics in cystadenocarcinoma, another type of metastasis occurs with both benign and malignant cystadenomas—implantation metastases. If the cyst ruptures spontaneously, or if during the surgical removal, epithelial cells enter the peritoneal cavity, they will attach to the peritoneum, survive, and grow as a tumor. With the serous cyst, there are numerous papillomas attached to the

abdominal wall and to the intestine, and the peritoneal cavity is filled with a clear fluid. With the pseudomucinous variety there are the same papillomatous masses, but the peritoneal cavity is filled with a thick viscid mucus, a condition known as “pseudomyxoma peritonei” (Tauber).

FIBROMA OF THE OVARY

Pathologic Anatomy. The fibroma of the ovary is a unilateral, rarely bilateral, firm, lobulated tumor, 5 to 15 cm. in diameter. Section shows that it is composed of white interlacing

sharp line of distinction, and that within any one tumor all three types of cells may be found, usually with one as the dominant type.

Pathologic Anatomy. Granulosa Cell Tumor. The tumor composed largely of granulosa cells is an encapsulated, firm, smooth or lobulated mass, which on cut sections presents a yellowish gray, finely granular surface. Areas of hemorrhage and of cyst formation resulting from necrosis are common. The tumor cells microscopically resemble closely the granulosa cells of the normal graafian follicle. There is a small, oval, or round, hyperchromatic nu-



Fig. 429. Granulosa cell tumor of ovary with hyperplasia of endometrium. (Photograph by courtesy of Dr. Lauren Ackerman.)

bundles, with occasional areas of necrosis with cyst formation. The tumor is made up of fibroblasts, with a moderate amount of intercellular collagen. The fibroblasts are arranged irregularly, and show no tendency to palisading or whorl formation, although there are indefinite bundles.

Clinicopathologic Correlation. Meigs' Syndrome. The great majority of patients with a fibroma of the ovary complain of nothing more than a mass in the lower abdomen. A small percentage have associated ascites and hydrothorax—Meigs' syndrome. The age incidence is thirty-three to sixty-four years (Meigs, Armstrong, and Hamilton).

GRANULOSA CELL, THECA CELL, AND LUTEIN CELL TUMORS OF THE OVARY

In the early study of tumors of the ovary it was customary to speak of three distinctive types of tumors: granulosa cell, theca cell, and lutein cell tumors. With more intensive study, it became apparent that there is no

cleus surrounded by a scanty, faintly acidophilic cytoplasm. Within the cytoplasm of many of the cells there are numerous minute vacuoles filled with fat. With silver stains, little reticulum between the cells is demonstrable.

Theca Cell Tumor. Tumors composed for the most part of theca cells are firm and white, and on section show fibrillary whorled structure. Individual cells are fusiform and arranged in irregular interlacing patterns. With specific stains numerous intracellular fibrils may be demonstrated. The nucleus is elongated, and mitoses are rare. In a few areas one cell or a group of cells are differentiated to resemble epithelium. With silver stains an abundant coarse reticulum is observed between the cells. Many of the cells are filled with vacuoles of fat. The presence of histochemically demonstrable ketosteroid in the theca cells of these tumors correlates with functional hormonal disturbances (McKay, Robinson, and Hertig).

Lutein Cell Tumor. The lutein cell tumor is a solid, encapsulated, moderately firm, yellow mass within or replacing the ovary. A small pyknotic nucleus and an abundant finely vacuolated cytoplasm are observed microscopically (Traut and Butterworth; Traut, Kuder, and Cadden).

About 20 per cent of the granulosa cell tumors are malignant and give metastases in the regional lymph nodes, in the lungs, and throughout the body. They are moderately radiosensitive.

mer). About 60 per cent of the observed tumors occur after the menopause.

Clinicopathologic Correlation. The symptoms and signs are referable to two general phenomena: the presence of a palpable tumor in the pelvis, and the endocrine secretions of the tumor. The effect of the excessive estrogen depends on the stage of the sexual life of the woman. Before puberty there are the changes of precocious puberty (Stabler and Thomson). During adulthood there is amenorrhea sometimes followed by metrorrhagia, sterility,

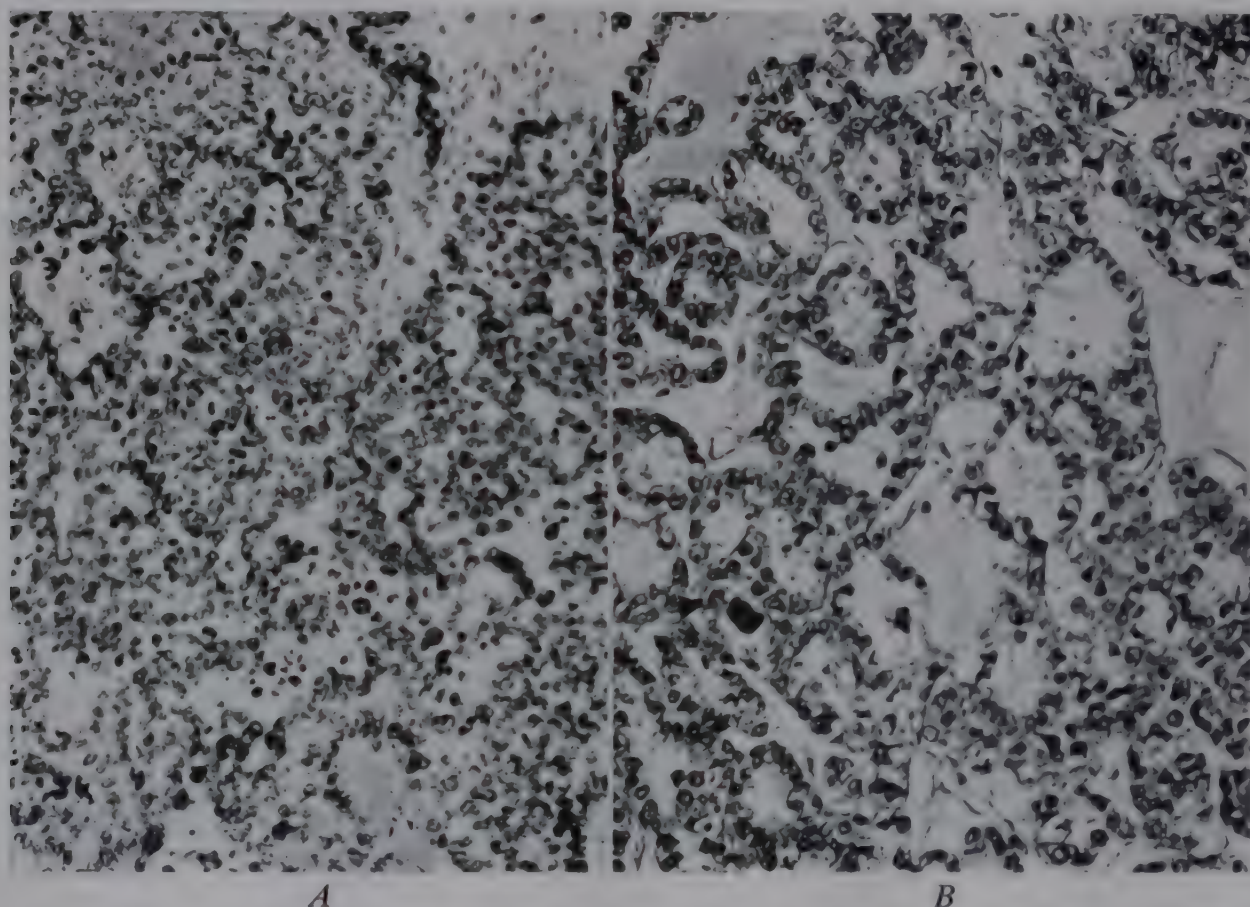


Fig. 430. *A*, Granulosa cell tumor. *B*, Arrhenoblastoma of the testicular tubular adenoma type. (Slides by courtesy of Dr. John Hobbs.)

Histogenesis and Causal Factors. It is now generally accepted that rests of undifferentiated gonadal tissue and the cells of the adult graafian follicle may give rise to the functional ovarian tumors. The cause is entirely unknown.

Hormonal Relations. The endometrium shows cystic hyperplasia and occasionally the picture of a premenstrual or menstrual change, indicative of hypersecretion of estrogen by the tumor. In a postmenopausal woman with atrophy of breasts, there may be hyperplasia. Assay of the urine shows variation from normal values to 17,000 mouse units per liter of urine. Quantitative study of the tumor tissue has shown values up to 20,000 international units per kilogram calculated as estrone (Pal-

and enlargement of the uterus. After the menopause there is reinstitution of periodic pseudomenstrual bleeding. Myoma of the uterus and carcinoma of the body of the uterus are commoner in these patients than in the general population (Stohr). About 10 per cent of the tumors are bilateral.

ARRHENOBLASTOMA

Pathologic Anatomy. These tumors are spherical or lobulated masses, with a definite gray capsule. They are composed of a gray, fibrillar, interlacing network of trabeculae, inclosing variable-sized nodules of yellow or reddish yellow, soft, bulging tissue. The tumor cells are polygonal or columnar, or spindle-shaped, arranged in one of three patterns. The

columnar cells may be arranged into definite tubular or alveolar structures—"testicular tubular adenoma." The spindle-shaped cells may be arranged irregularly and resemble a sarcoma. A third pattern is represented by solid cords or strands of polygonal cells without lumens. In any one tumor various fields may show mixtures of these three cellular patterns (Dockerty and MacCarty).

Histogenesis. It is generally accepted that the arrhenoblastoma is derived from the undifferentiated gonadal cells known as the "rete ovarii" (Meyer).

tumor of the ovary, the adenoma or carcinoma of the adrenal cortex, and the basophilic adenoma of the pituitary gland.

DYSGERMINOMA OF THE OVARY

The dysgerminoma is delineated on the basis of a histologic resemblance to the seminoma of the testis, and the absence of functional activity. The tumors are large and nodular, and are completely enveloped in a fibrous tissue capsule. They are firm, elastic, and grayish white, and are composed of broad sheets and columns of large round cells, with an abun-

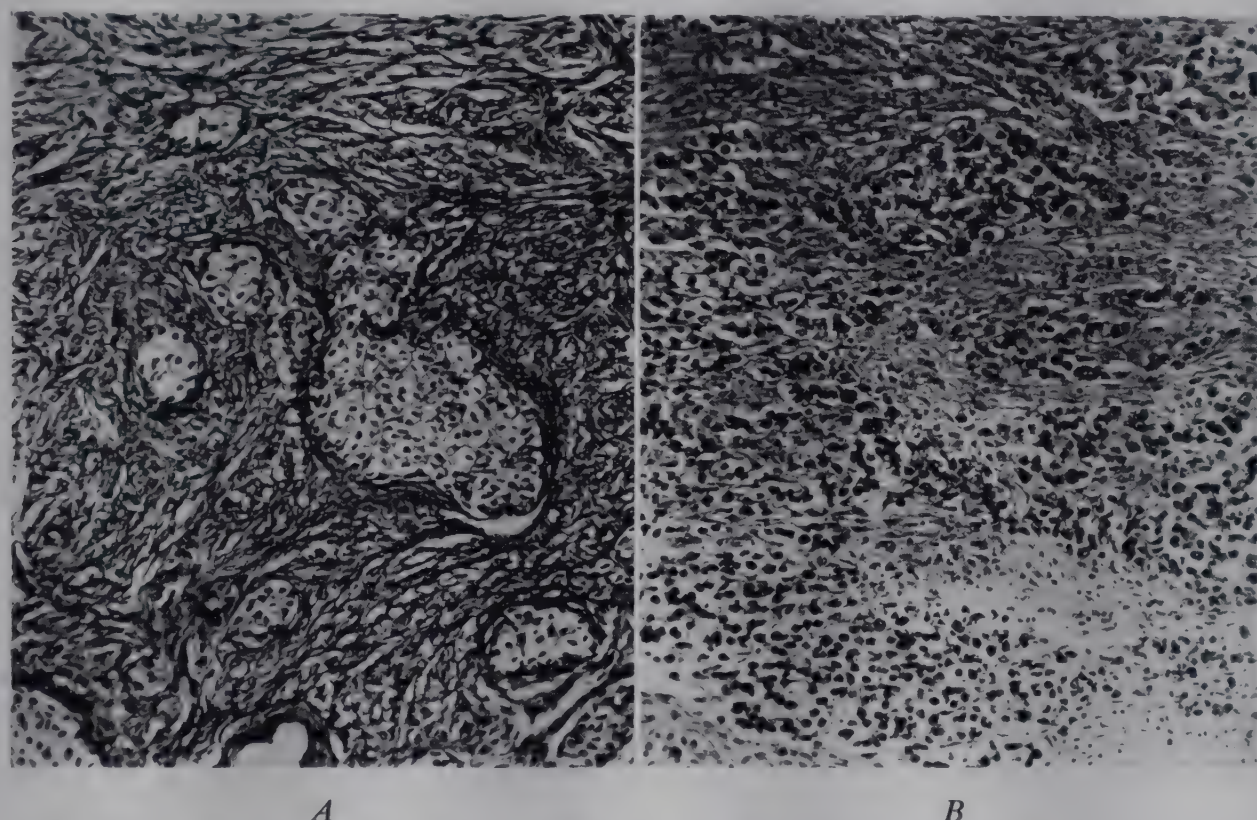


Fig. 431. *A*, Brenner tumor of ovary. *B*, Dysgerminoma of the ovary.

Clinicopathologic Correlation. Women with this tumor show defeminization (atrophy of the breasts, suppression of menstruation, and partial loss of the hair of the head) and masculinization (growth of a beard, change of the voice, growth of hair on the body, change of the pubic hair to a male type, and development of the male configuration of the body).

Gynandroblastomas. Rarely there is a combination of a granulosa or theca cell tumor and an arrhenoblastoma. The patient shows a mixture of feminization and masculinization (Hobbs).

Masculinizing Tumors in Women. The arrhenoblastoma is only one of the several tumors occurring in women which bring about masculinization or sex reversal. The other more important tumors are the adrenal cell

dant, lightly acidophilic cytoplasm, and hyperchromatic nuclei. Mitoses are numerous. The cells of the tumor are separated by delicate strands of connective tissue infiltrated with lymphocytes. In many areas there are small collections of epithelioid cells and giant cells which resemble tubercles.

Dysgerminoma occurs most frequently in the right ovary, and in patients below the age of twenty years. It is probably derived from undifferentiated mesenchyme in the primitive gonad, at a stage before sexual differentiation. Most dysgerminomas are benign, and removal results in complete cure (Sailer).

BRENNER TUMORS OF THE OVARY

Pathologic Anatomy. The Brenner tumor of the ovary is a solid, firm, spherical or nod-

ular tumor, with little tendency to necrosis, hemorrhage, or formation of cysts. There is no definite capsule, but about the edge of the tumor a small amount of compressed ovarian stroma may usually be identified. There are two characteristic cells, a stromal cell and an epithelial cell. The *stromal cells* are well-developed, spindle-shaped fibroblasts, with a moderate amount of intercellular collagen. These cells are formed in broad and thin trabeculae enclosing irregular masses of the epithelial element. The *epithelial cells* are typically cells resembling squamous epithelial cells, but in some places they are columnar cells enclosing a small cystic space. Each cell has a large amount of cytoplasm and a small nucleus. Mitotic figures are rare. The centers of many epithelial masses undergo liquefaction (Novak and Jones; Jondahl, Dockerty, and Randall).

Incidence. The Brenner tumor occurs most frequently in women beyond the menopause.

Histogenesis. It is generally accepted that the Brenner tumor is derived from small epithelial inclusions near the hilum of the ovary, known as "Walthard inclusions."

Clinicopathologic Correlation. The Brenner tumor of the ovary is devoid of functional activity, and the only expected sign or symptom is the presence of a mass in the pelvis. The tumors are benign and occasionally associated with ascites.

ADRENAL CELL CARCINOMA OF THE OVARY

Rarely, a tumor identical in gross and microscopic structure with the epithelial cortex of the adrenal occurs in the ovary. These tumors form large, encapsulated, moderately firm masses, completely replacing one ovary. They are yellow and show the typical areas of necrosis, cyst formation, and hemorrhage. The cells are arranged irregularly or in columns, with a scant amount of interstitial connective tissue, and abundant thin-walled capillaries. The individual cells have a small, moderately chromatic nucleus, and a clear or highly vacuolated cytoplasm. These tumors are associated with masculinization (Van Kirk and Edwards).

UNCLASSIFIED CARCINOMA OF THE OVARY

Some epithelial tumors of the ovary cannot be classified into definite types. These are

usually designated as "unclassified carcinoma," "undifferentiated carcinoma," or "solid ovarian carcinoma."

Pathologic Anatomy. This type of tumor is bilateral in about 40 per cent of cases, and occurs as a solid, firm, lobulated or smooth mass varying from a few centimeters in diameter to a size sufficient to fill the pelvis. The ovary is completely destroyed and replaced by tumor. The tissue is grayish white, with many minute grayish yellow areas. Foci of hemorrhage, necrosis, and cyst formation are not uncommon. In advanced cases the tumor becomes adherent to the surrounding viscera and invades the peritoneum. The peritoneal cavity contains an excessive amount of fluid.

The tumor tissue is composed of an abundant fibrous-tissue stroma with islands, columns, and cords of atypical epithelial cells. The commonest type is carcinoma simplex, but adenocarcinoma and mucinous carcinoma are observed.

Histogenesis. The origin of the solid ovarian carcinoma is obscure. Some of the solid tumors are probably papillary cystadenocarcinomas in which the cyst never developed or was filled with tumor cells.

Incidence and Causal Factors. The ovarian carcinoma, including all types, both cystic and solid, constitutes about 5 per cent of all malignant tumors in women (Stout). The tumors are commonest during the fifth and sixth decades, and 40 per cent occur in women after the menopause. Of married women who develop ovarian carcinoma, 35 per cent have never been pregnant, and 42 per cent give a history of one or more abortions. The tumor occurs slightly more frequently in unmarried women than would be indicated by the proportion of these in the general population (Murphy; Lynch). A history of cancer in the family is secured in 10 to 20 per cent of patients.

Clinicopathologic Correlation. The signs and symptoms are in general neither compelling nor serious. A tumor produces an increase in the size of the abdomen, ascites, and pressure on the gastro-intestinal tract. Pain is a common early symptom, possibly from pressure on the nerve trunks or from invasion of the perineural lymphatic spaces. These tumors do not secrete any demonstrable hormone, yet they are frequently associated with abnormal uterine bleeding. The solid ovarian tumor is the most malignant. The life expectancy does

not exceed sixteen months, and the percentage of five-year cures is less than 10 per cent (Jacobs). The cystic tumors have a far better prognosis, averaging 35 per cent five-year survivals.

METASTATIC TUMORS OF THE OVARY— KRUKENBERG'S TUMOR

In some cases of carcinoma of the upper abdominal organs, of the breast, and rarely of other organs, there is bilateral enlargement of the ovaries and replacement of them by a characteristic type of neoplastic cell. The ovaries are large, slightly lobulated, grayish white, and firm. Throughout a dense, connective-tissue stroma, there are isolated groups of signet-ring cells. The nucleus of the cell is small and chromatic, and is pushed to one side by a large vacuole, filled with a small amount of stringy, basophilic material (Leffel, Masson, and Dockerty). This is the description originally given by Krukenberg, whose name is attached to this type of tumor. About as frequently, bilateral metastatic tumors of the ovary are observed in which the cellular tissue does not correspond to this original description, but in which the process is essentially the same. The preponderance of morphologic evidence indicates that the tumor cells are disseminated by implantation within the peritoneal cavity (Woodall). Other types of metastatic carcinoma and sarcoma in the ovary are rare.

DERMOID CYST AND TERATOMA OF THE OVARY

A dermoid cyst was formerly defined as a "cystic tumor composed of tissues derived from the ectoderm." A teratoma on the other hand is a tumor containing the elements from two or more germ layers. There seems little justification today for separating the two. Multiple sections from all parts of the so-called "dermoid cyst" will demonstrate small islands of tissue which may be termed "nonectodermal."

Pathologic Anatomy. The usual teratoma of the ovary is a unilateral (rarely a bilateral), solid or cystic tumor, 5 to 10 cm. in diameter, completely replacing the ovary or stretching the ovarian tissue over the surface of a part of the tumor. The cysts are filled with a clear or bloody fluid. In what is usually termed the "dermoid cyst," there is a wall 3 to 4 mm. in

thickness about a single cavity. This cavity is filled with a thick cloudy fluid, in which there are suspended numerous droplets of fat, cholesterol crystals, and hairs. At one point on the inner lining of the cyst there is a small germinal tubercle, 2 to 4 mm. in height. From this tubercle numerous hairs project. If a tooth is present, it will be embedded or project from the tubercle.

Microscopic section of the teratoma may show any tissue in the body, either embryonic or adult, except the gonad. Tissues from the alimentary and the respiratory tracts are most regularly present. These consist of mucous glands, small segments of the intestine with a definite lumen, or rarely a short loop of the intestine, identifiably grossly as well as microscopically. Elements of the nervous system are consistently found as small masses of glial tissue with an occasional ganglion cell and as myelinated nerves. Bone and cartilage are common constituents. Between the trabeculae of the bone there may be well developed functional bone marrow, with cells of both the red and the white cell series. Smooth or skeletal muscle may be present independently, or in association with the attempted duplication of some structure normally possessing these elements. Filling in between these more differentiated tissues are large amounts of fibrous tissue and adipose tissue. The typical constituents of the dermoid cyst are the squamous epithelium which lines the cavity and sebaceous and sweat glands within the fibrous-tissue wall (Nicholson).

Histogenesis and Causal Factors. The exact mode of origin of teratoma of the ovary is unknown. The following theories have been proposed: internal twinning, proliferation of dislocated or supernumary blastomeres, growth of fertilized polar bodies, parthenogenesis of gonadal or extragonadal germ cells, and developmental errors in the primitive streak and early axial structures. Careful morphologic studies indicate that the elements are not growing indiscriminately, but that one type of tissue growth influences the differentiation of another tissue. For example, about structures which appear as a bronchus, cartilage regularly appears, and about teeth bone is usually present (Willis). This has suggested a relation to the tissue organizers of Spielmeier (Kafka).

Clinicopathologic Correlation. None of the

teratomas, except the rare choriocarcinoma, is associated with increased excretion of gonadotropin in the urine. There remains then only the presence of a tumor in the pelvis as a basis for the diagnosis. Tumors may be found at any age, but are commoner in late life. They are seldom malignant. Metastases of the malignant varieties are to the regional lymph nodes,

ous papillae. They may be found at any age and are commoner in the right than in the left ovary (Schiller).

Sarcoma. The greater number of sarcomas of the ovary reported in the literature were studied before the modern concepts of functional ovarian tumors had been enunciated by Robert Meyer. Many of them are undoubtedly

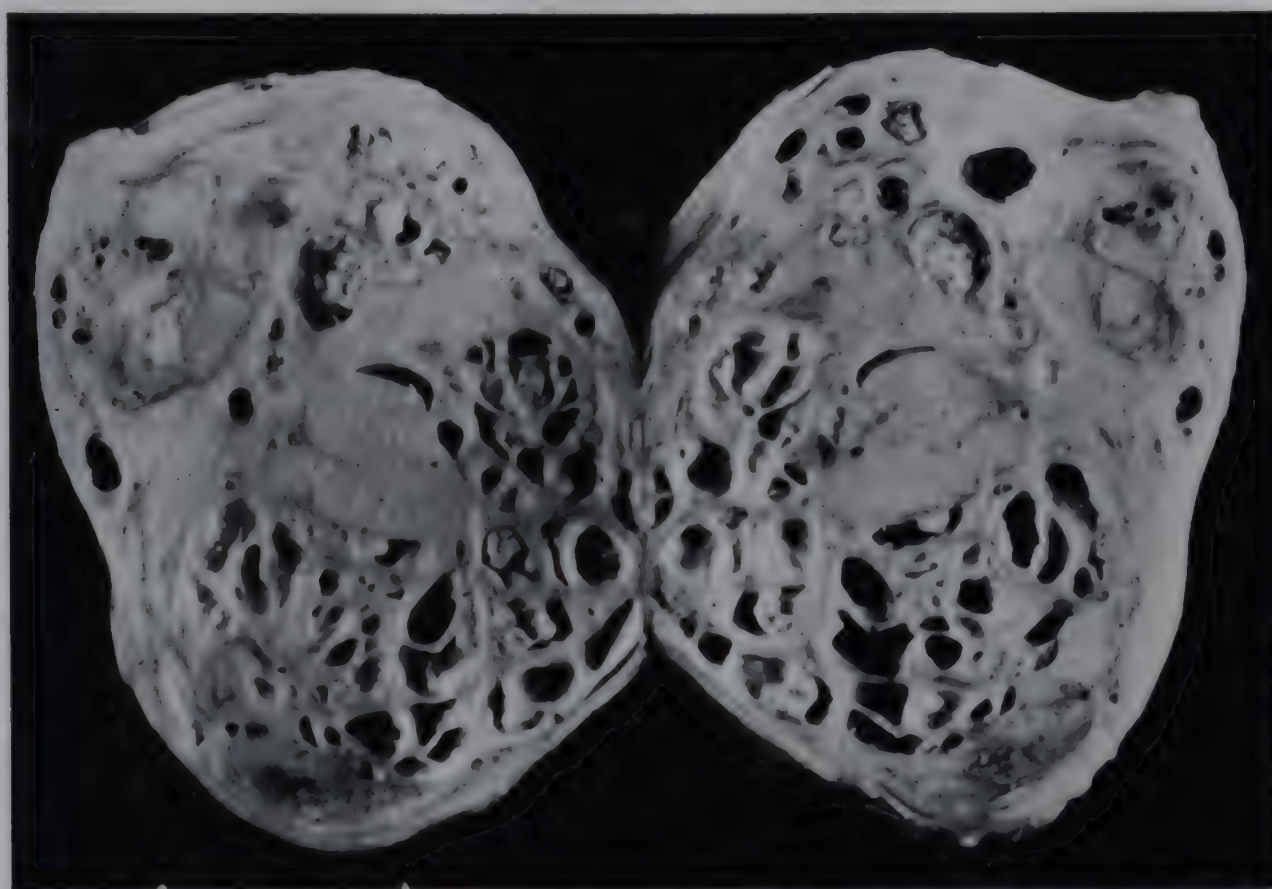


Fig. 432. Adult type of teratoma of the testis.

to the lungs, and subsequently to most of the organs and structures in the body.

Struma Ovarii. In some teratomas there are small islands of thyroidal tissue, but in a few the greater mass is composed of typical acini filled with colloid. This variety of teratoma is generally known as "struma ovarii" (Sailer). It constitutes from 4 to 15 per cent of all teratomas. There are well authenticated cases in which removal of an ovarian tumor has cured a patient of hyperthyroidism (Emge).

MISCELLANEOUS TUMORS OF THE OVARY

Mesonephroma. These are rare cystic tumors in which the epithelial lining is made up of an irregular single line of projecting epithelial cells, with a prominent nucleus and a narrow rim of cytoplasm. Into the microscopic cysts small glomerulus-like bodies project, and in the connective tissue between cysts there are abortive tubules and a primitive type of mesenchyme, reminiscent of the developing mesonephros. In the larger cysts there are numer-

ous theca cell tumors. It seems best to withhold judgment until a comprehensive morphologic study can be made (Scheffey).

The Testis

TERATOMA OF THE TESTIS

Pathologic Anatomy. About 97 per cent of all tumors of the testis are of the teratoid variety. These tumors are composed of four cellular types: adult teratoma, seminoma, embryonal carcinoma, and choriocarcinoma.

Adult Teratoma. The teratoma is a firm tumor with small cysts, islands of cartilage, and yellow and white flecks visible on the cut surface. The more common components are squamous epithelium, columnar epithelium, cartilage, and smooth muscle. In most part the various tissues are organized into structures such as alimentary tract, stomodeal elements, respiratory tract, and brain.

Seminoma. This is a distinctive type of tumor which grossly is gray and soft without

necrosis or hemorrhage. The cells are polygonal with prominent adjacent cell walls, clear cytoplasm, and a prominent nucleus containing a nucleolus. The stroma is arranged in trabeculae and infiltrated with a variable number of lymphocytes.

Embryonal Carcinoma. The cellular type shows great variation in pattern but is basically a large cell with indefinite cell walls, vacuolated or reticulated basophilic cytoplasm, and anaplastic nuclei. The pattern may be solid or papillary. In many embryonal carcinomas

chorionic epithelium, and the probable identity of the cell of embryonal carcinoma as a cytotrophoblast, suggest origin from a totipotent cell—the sex cell.

Causal Factors. Many have suggested that trauma is a causal factor but there is no convincing evidence. Tumors of undescended testes in the canal and in the abdomen are more common than those in scrotal testes (Gordon-Taylor and Till).

Hormonal Relations. All patients with a testicular tumor have a slight increase of pitu-

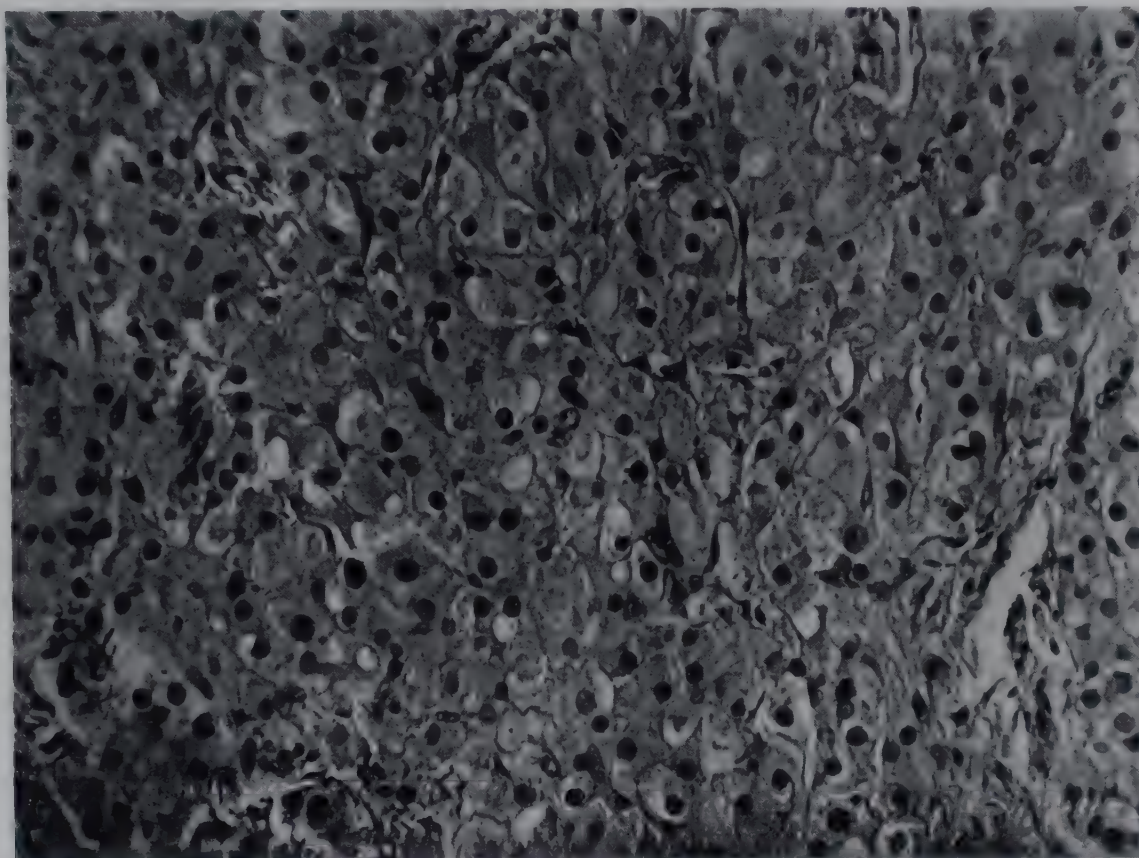


Fig. 433. Interstitial cell tumor of the testis. (Slide by courtesy of Dr. W. A. D. Anderson from the case reported by Werner, Spector, Vitt, Ross, and Anderson: *J. Clin. Endocrinology*, Vol. 2.)

there are associated immature somatic elements and rarely structures which are identical with early stages of the human embryo. Grossly this tumor is large and bulky with large and small foci of necrosis and hemorrhage.

Choriocarcinoma. This tumor in the testis is identical in structure with that in other organs. It is a red, soft mass and contains variable degrees of organization of the cytotrophoblasts and syncytiotrophoblasts.

Mixed Types. Most tumors of the testis consist of two or three of the four cellular types. The most common is the mixture of embryonal carcinoma and teratoma known as teratocarcinoma (Friedman and Moore).

Histogenesis. The presence of embryos, of immature and mature somatic tissues, and of

itary gonadotropin in the urine, but there is excessive excretion of chorionic gonadotropin in those with an embryonal carcinoma or choriocarcinoma, and rarely with a seminoma. The pituitary may show the same changes as in pregnancy (Entwisle and Hepp) and in a few patients there is gynecomastia (Cooke).

Clinicopathologic Correlation. There are rarely signs or symptoms except those of a tumor mass. After adequate therapy with surgery and/or x-ray the five-year survival rates are for teratoma 75 per cent, for seminoma 90 per cent, for embryonal carcinoma 30 per cent, and for choriocarcinoma less than 20 per cent.

Experimental Production. The injection of a solution of zinc sulfate into the testes of

chickens in the springtime occasionally results in teratoma. Similar results can be secured if the chickens are injected simultaneously with gonadotropic hormone (Bagg). The occurrence of the teratoma in man during adult sexual life, together with these observations in birds, indicates that one of the causal factors may be hormonal.

HYPERPLASIA AND TUMORS OF THE INTERSTITIAL CELLS OF THE TESTIS

In a great variety of conditions, histologic examination of the testis reveals an apparent increase in the number and size of the interstitial cells. In almost all of these conditions there is associated atrophy of the testis as a whole, affecting particularly the seminiferous tubules. This may not represent true hyperplasia, since the collapse of the seminiferous tubules would condense the interstitial cells and render them more conspicuous.

Pathologic Anatomy. Despite this doubt about hyperplasia, there can be no question concerning tumors of the interstitial cells. They are usually of moderate size, and are composed of lobules of yellowish red, soft tissue, separated by connective-tissue trabeculae. The individual cells are polymorphous and arranged in small or large groups by fibrous septa. The cytoplasm is homogeneous or granular, and contains numerous vacuoles of fat, of pigment, and of refractile granules. The nuclei are relatively small and vesicular, with one or two prominent nucleoli. The cells are arranged irregularly or in definite columns, similar to those in the normal adrenal gland. They are usually benign, although metastases have been reported (Jemerin; Warren and Olshausen).

Clinicopathologic Correlation. This tumor is extremely rare. In adults the condition is not infrequently associated with gynecomastia (Hunt and Budd). In prepuberal children there is precocious sexual development (Stewart, Bell, and Roehlke). Similar tumors have been reported in animals, especially dogs (Schlotthauer, McDonald, and Bollman). Long-continued injection of estrogenic hormones into certain strains of male mice (A strain of Strong) results in a few examples of both benign and malignant tumors of the interstitial cells of the testis (Hooker, Gardner, and Pfeiffer).

MISCELLANEOUS TUMORS OF THE TESTIS AND TESTICULAR APPENDAGES AND TUNICS

Aside from the teratoma described in the foregoing, tumors of the testis, of the epididymis, of the spermatic cord, and of the testicular tunics are rare. The more important are the lipoma, fibroma, and leiomyoma, together with the corresponding malignant types. They are identical in structure with similar tumors in other parts of the body (Thompson).

A distinctive tumor of the epididymis is composed of epithelium-like cells arranged in an alveolar pattern within a connective tissue stroma. The individual cells are richly vacuolated or arranged in an acinus. Origin from mesothelium, epithelium, and lymphatic endothelium has been postulated. The best designation at present is adenomatoid tumor.

CRYPTORCHIDISM

Pathologic Anatomy. Cryptorchidism is a condition in which one or both testes are not located in their normal position in the bottom of the scrotum. They may be found within the inguinal canal, at the internal ring, in the abdomen, in the perineum, or in the tissue of the upper part of the thigh. The cryptorchid testis is on an average one-half to two-thirds as large as the normal testis, and the capsule is wrinkled. The epididymis is frequently completely separated by the mesorchium.

The basement membranes of the seminiferous tubules are thickened and hyalinized. The tubules are lined by a single layer of cuboidal Sertoli cells. Occasionally for a few years after puberty the tubules contain spermatogonia and spermatids, but never spermatozoa. The interstitial tissue is compact, and the interstitial cells of Leydig are conspicuous, but not increased in number. The blood supply and nerve supply to the cryptorchid testis are normal. The cryptorchid testis in a prepuberal boy does not differ in histologic structure from the normally descended testis.

Causal Factors. Adhesions of the testis to abdominal structures may prevent its descent; and clinical studies indicate that there are anatomic impediments more often than there is a lack of endocrine stimulus. These anatomic abnormalities may involve the mesorchium, the gubernaculum, the cremasteric muscle, or the vaginal process. Inguinal hernia is a frequently associated lesion. Some success in

treatment by injection of gonadotropins has been reported (Thompson and Heckel).

Hormonal Status and Clinical Considerations. The absence of spermatogenesis in the cryptorchid testis is responsible for sterility. The fact that the temperature in the abdomen is higher than that in the scrotum is undoubtedly responsible for the lack of spermatogenesis (Moore). The decreased secretion of androgen by the cryptorchid testis (Korenchevsky) may be reflected in a lack of full development of the secondary sexual characteristics. The relation of the cryptorchid testis to the development of the teratoma has been discussed.

Descent of the Ovary in Women. Rarely, the ovaries descend into a vaginal process contained within the labia majora.

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CII

Diseases of the Female Secondary Sexual Organs

The female secondary sexual organs may be arranged in two groups: the pelvic sexual organs and the breast. Diseases of the pelvic sexual organs are discussed in this chapter, and diseases of the breast in Chapter CIII, p. 915.

Congenital Anomalies. The greater part of the female genital tract is formed from the two

Diseases of the Vulva

The important specific inflammations of the vulva have been considered in the chapters on venereal disease.

Vulvar Kraurosis. In this condition the subcutaneous fat of the mons pubis and labia disappears, the epidermis of the vulva becomes



Fig. 434. Leukoplakia of vulva.

müllerian ducts. In the lower part, they fuse completely to form the upper segment of the vagina, the cervix, and the uterus. In the upper part they remain separate, as the uterine tubes. Complete agenesis results in absence of the vagina, uterus, and uterine tubes. Failure of union of the ducts may be of any degree, so that duplication of the entire tract from the vagina upward, duplication of the cervix and uterus, and duplication of the fundus are observed. Absence of the vagina is usually associated with absence of the uterus and tubes.

thin and mottled red and white, the clitoris and prepuce atrophy, and there is marked contraction of the vulvar orifice, even to the point of dyspareunia. The surface is dry, and fissures may form. Secondary inflammation of the atrophic tissues leads to edema and cellular infiltration (Graves and Smith).

The incidence of kraurosis in postmenopausal women, and in those who have had ovariectomy or been subject to intensive treatment with radiant energy, suggests that the atrophy results from hypo-estrinism.

Vulvar Leukoplakia. *Pathologic Anatomy.* Leukoplakia is characterized by diffuse or focal, often symmetrical, translucent, white thickening of the vulva. The dermis is devoid of elastic tissue, and condensation of collagen may form a prominent hyaline membrane beneath the epidermis. The epithelium is typically hyperplastic, with acanthosis, prominent keratin granules, and hyperkeratosis. There are numerous cells in mitosis. The rete are broadened and elongated. Less typically there

cause genital or anal pruritus include urethral and periurethral infections, dribbling of an acid urine, leukorrhea, chronic vaginitis and cervicitis, irritation from pads worn to absorb the menstrual bleeding, accumulation of smegma in crevices about the genitalia, hemorrhoids, inflammation and fissures of the recto-anal canal, and soiling of the skin with feces. The chief systemic factors are disturbances in hormonal balance, such as occur during the menstrual cycle and the menopause.

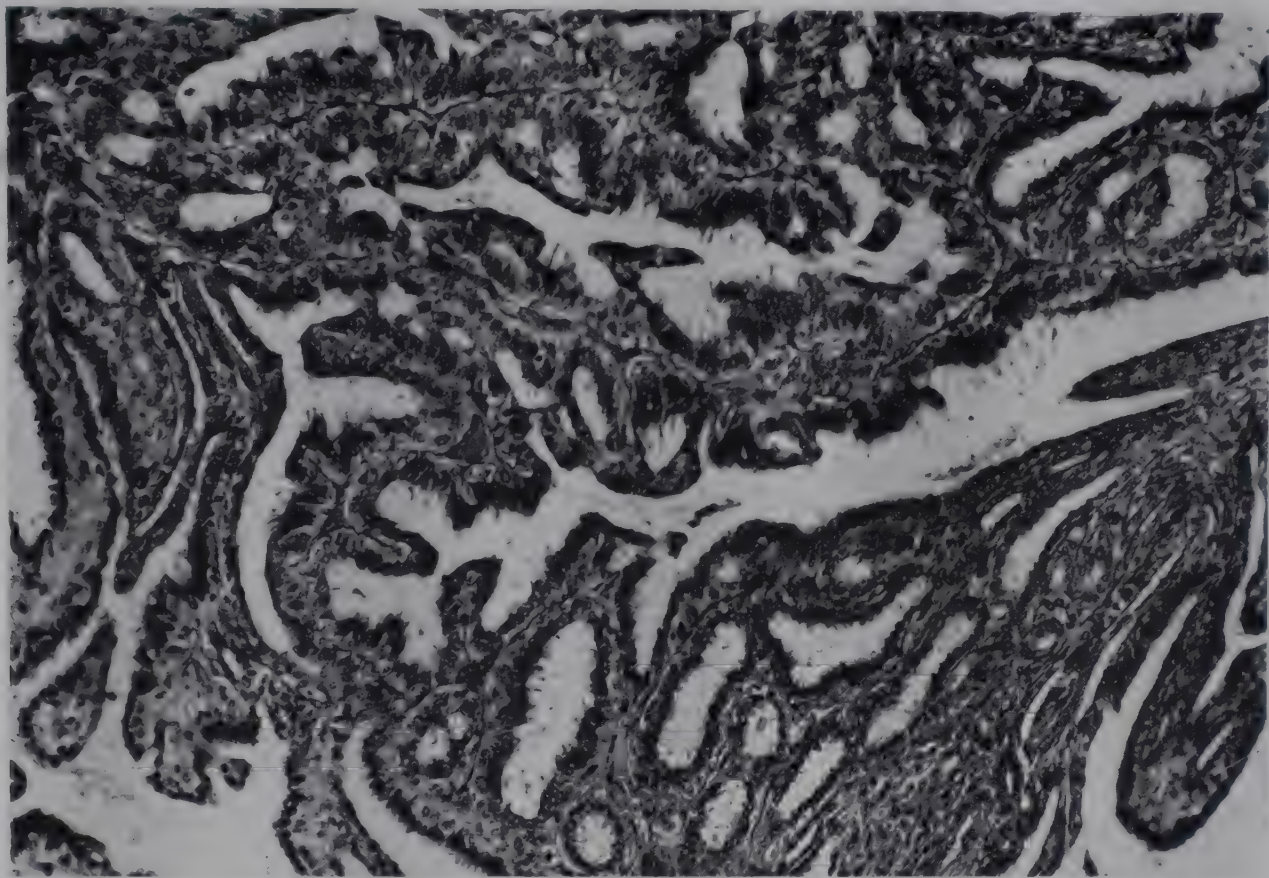


Fig. 435. Hidradenoma of vulva. (Slide by courtesy of Dr. John Hobbs.)

is diffuse or focal atrophy of the epidermis, as well as fibrosis of the dermis. Secondary inflammation leads to infiltration of cells and cicatricial contraction of the entire vulva (Montgomery, Counseller, and Craig).

Significance. About one-half of all vulvar carcinomas arise in a leukoplakia (Taussig).

Genital and Anal Pruritus. Pruritus, or itching, about the genitalia and anus is a symptom and not a disease entity (Savill).

Pathologic Anatomy. The anatomic changes in the tissue are in general those of mild inflammation, based both on the ultimate cause and on trauma from scratching. In some types—postmenopausal—there is atrophy of the epidermis, while in others there is hyperplasia. Pustules, primary as in a seborrheic dermatitis and follicular infections, or secondary to scratching, are seen.

Causal Factors. Local factors which may

Benign Tumors. Benign tumors of the vulva include fibroma, leiomyoma, angioma, papilloma, and lipoma (Lovelady, McDonald, and Waugh). Cysts may arise in Bartholin's glands or from remnants of the wolffian ducts in the labia, clitoris, and hymen. In addition there are two distinctive types, urethral caruncle and hidradenoma.

Urethral Caruncle. The term "caruncle" is a generic designation for a small, painful nodule about or in the external urethral orifice. Some show hyperplastic, squamous epithelium, covering a loose or dense fibrous stroma. Others have a similar structure except that the stroma contains numerous vascular spaces. Still others are infiltrated with cells, and are apparently inflammatory in origin (Walther).

Hidradenoma. The hidradenoma is a small, sessile or pedunculated, circumscribed nodule, usually on the labia majora. There are numer-

ous small and large glands and ducts lined by nonciliated columnar cells with clear cytoplasm and hyperchromatic nuclei. Beneath this luminal layer are several irregular rows of polygonal or rounded cells. They originate in the apocrine glands (McDonald).

Malignant Tumors. Carcinoma of the vulva is most common on the labia and in the sixth decade. Growth is slow but ulceration occurs early and fungating masses are formed. The microscopic structure is that of an epidermoid carcinoma. Granulomatous venereal lesions and leukoplakia are associated lesions. The five-year survival rate is about 20 per cent

Injuries of the supporting structures of the vaginal wall may allow the intra-abdominal pressure to force other organs into the vaginal cavity: the bladder through a relaxed vaginovesical septum and separated anterior leaf of the broad ligament (cystocele); the rectum through separated levator ani muscles and the triangular perineal ligament (rectocele); and the intestine through the posterior vaginal vault in a weak spot in the uterosacral ligaments (enterocele).

Laceration of the perineum may involve the vagina (first degree), the superficial perineal fascia of Colles, the triangular ligament,



Fig. 436. Cervical erosion. (Curtis.)

(Lunin). Adenocarcinomas originate in Bartholin's gland (McDonald, Lovelady and Waugh).

Miscellaneous Tumors. Sarcoma and malignant melanoma of the vulva are reported (Taussig). Metastatic tumors are rare (Taussig). Sarcoma is prone to recur and metastasize widely. The prognosis is poor. Of the cellular types, fibrosarcoma and myxosarcoma are the more common.

Injuries of the Vagina and Uterus

As the uterus enlarges in pregnancy, certain tissues and structures are stretched, and during the passage of the fetus through the birth canal, the same and other structures are subjected to considerable trauma.

Pathologic Anatomy. The commonest type of injury is *laceration of the cervix*. Laterally, there are deep fissures in the wall. With healing, epithelization and fibrosis take place. Contraction of the fibrous tissue may roll the cervix outward (ectropion or eversion).

the levator ani muscles (second degree), and the sphincter ani (third degree).

Rupture of the uterine wall from the internal pressure generated by the contraction of labor is a grave obstetric complication. Rarely, as the placenta is delivered the uterus turns inside out and projects through the vagina (inversion of the uterus).

Significance. Cervical laceration may be the site of chronic inflammation with leukorrhea, and it plays a causal role in some cervical carcinomas (see p. 902). Pulling of the trigone of the bladder into a prolapse sac or a cystocele and injury of the vesicle sphincter lead to various urinary disturbances. The bladder may be unable to empty completely, and the residual urine may become infected. Laceration of the anal sphincter results in fecal incontinence.

Vaginal Fistulas

A fistulous opening between the female reproductive organs and a surrounding hollow viscus is most frequently seen in the vagina,

connecting with the bladder or rectum. The usual causes are necrosis of a malignant tumor which has invaded both structures, obstetric injury, and necrosis following irradiation.

In vesicovaginal fistula the urine is irritating to the vagina and circumvaginal skin, and chronic inflammation is established.

Leukorrhea—Vaginitis

The term "leukorrhea" signifies a white or yellow discharge from the vagina. It is caused by many different conditions and lesions, which may conveniently be arranged into three categories: physiologic, constitutional, and pathologic (Wharton). The *physiologic type* is seen just before or after menstruation, at the time of ovulation, during sexual excitement, and during pregnancy and the puerperium. *Constitutional leukorrhea* is apparently associated with excessive fatigue and debilitating illnesses. *Pathologic types* may result from lesions of any part of the genital tract. The important bacterial varieties—gonococcal, fusospirochetel, monilial, and trichomonal—have been discussed in other chapters. Lesions of the female genital tract, such as cervical erosion, subinvolution of the uterus, and inflammations and tumors of the uterus and tubes, will be considered in subsequent sections of this chapter. *Senile vaginitis* is a distinctive lesion seen in older women. The vaginal epithelium is atrophic.

Tumors of the Vagina

All tumors of the vagina are rare. Fibromas, leiomyomas, myxomas, and papillomas occur as sessile or pedunculated neoplasms. Endometriosis of the rectovaginal septum may project into the vagina.

Epidermoid carcinoma arises most frequently on the posterior wall of the upper half of the vagina, in women between thirty-five and fifty-five. The initial lesion is a nodule or papillary growth. With further growth and extension, adherence to the rectum and bladder is seen.

Sarcoma is an exceptional lesion. Most are fibrosarcomas or leiomyosarcomas. In children botryoid sarcoma is seen in the vagina.

Cervicitis—Cervical Erosion

Inflammation of the cervix is caused by

gonococci and by the bacteria normally present in the vagina, notably streptococci.

Cervicitis. The cervix is swollen and red. From the external os a quantity of thick mucosa or pus exudes. The tissues are infiltrated with leukocytes and fewer numbers of lymphocytes and plasma cells. If the swelling is great, a part of the cervical canal may be turned out—eversion or ectropion. As the inflammation becomes chronic there is proliferation of fibrous tissue and fixation of the eversion, especially if there is an associated laceration. The dominant infiltrating cells are the lymphocyte and plasma cell (Maryan).

Nabothian Cysts. As a part of the inflammation the ducts of the glands may be occluded by detritus or fibrosis, and they may form small cysts, 1 to 5 mm. in diameter, projecting into the canal or onto the surface.

Cervical Erosion. In the true erosion, as distinguished from ectropion and from ulceration, the central part of the cervix is red and granular. It is covered by columnar or cuboidal cells in contrast with the normal stratified squamous. The subepithelial tissue is slightly edematous and hyperemic, and is infiltrated with lymphocytes.

The cause was formerly thought to be actual erosion by the acid secretions of the vagina and bacterial action. A more satisfactory theory is that there is an interplay between the squamous epithelium of the outer cervix and the columnar epithelium of the cervical canal. In the first stage of endocervicitis the cylindrical cells of the canal extend outward. As healing ensues, the squamous cells re-cover the cervix to the external os.

Epidermization in the Cervix. In many examples of chronic cervicitis and cervical erosion there are islands of squamous epithelium, formed either by extension downward of the surface epithelium or by metaplasia within the gland. The lesion is important largely because of possible confusion with carcinoma. The main points of difference are the regular outline of the islands of epithelium, and the lack of anaplasia and mitoses of the cells in epidermization (Carmichael and Jeaffreson).

Cervical Polyp

Pathologic Anatomy. Most cervical polyps arise from the endocervix of the canal and are pedunculated through the external os.

They are single or multiple, red, soft masses covered by cylindrical epithelium. The stroma is a loose connective tissue, and is set through with numerous glands, some of which may show epidermization, as in cervical erosion.

Polyps arising from the vaginal surface of the cervix are gray and firm. The surface is covered by a squamous epithelium.

In both types ulceration and secondary inflammation or ischemic necrosis are common; hence the frequency of intermenstrual bleeding as a sign.

Significance of Cervical Polyps. Cervical polyps are a lesion of adult women. Nothing is known of causal factors. Occasionally carcinoma originates in a polyp (Geiger).

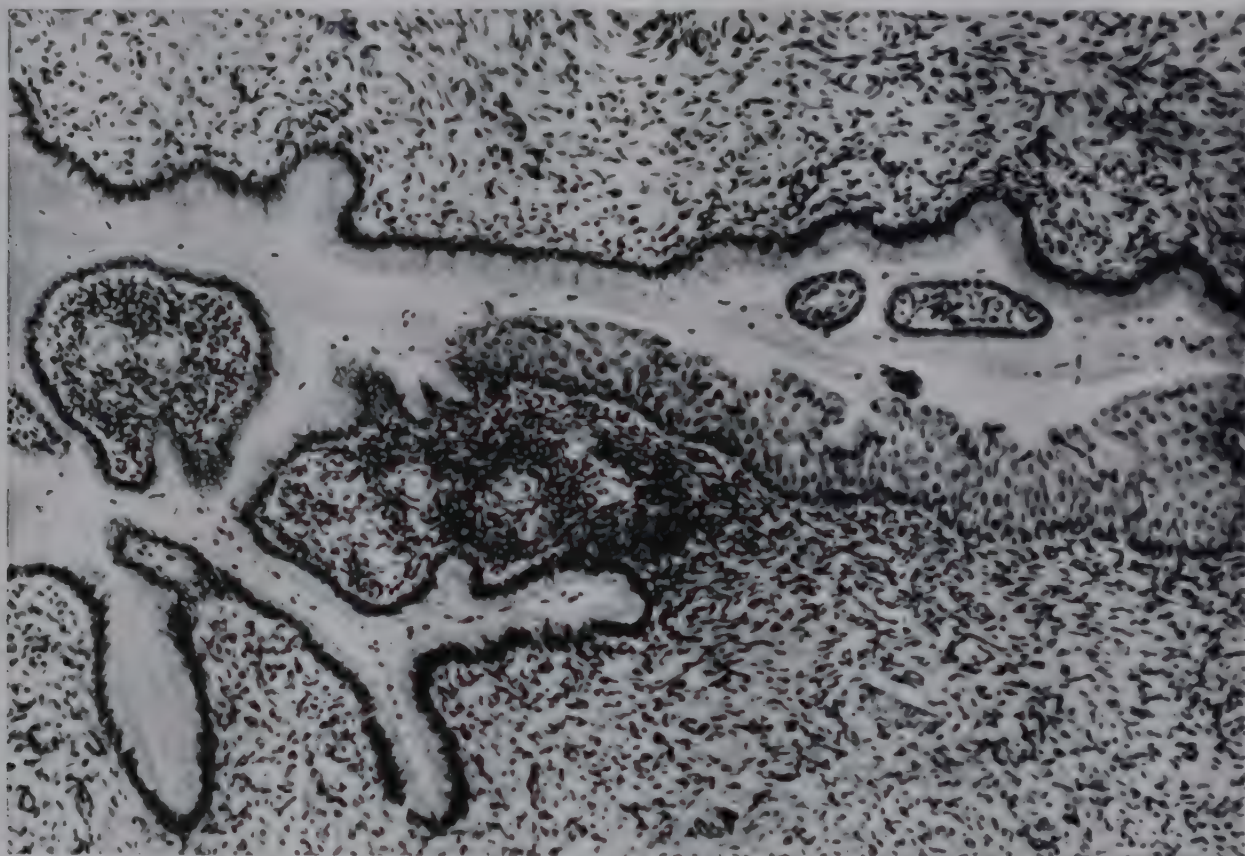


Fig. 437. Epidermization of cervical gland. (Slide by courtesy of Dr. John Hobbs.)

Carcinoma of the Cervix

Carcinoma of the uterine cervix constitutes 25 per cent of all carcinoma in women and causes the death of not less than 16,000 women each year in the United States.

Pathologic Anatomy. Early Stage (*Carcinoma in Situ*). The earliest stage of carcinoma of the cervix is characterized by anaplasia, basal cell hyperplasia, loss of polarity of the cells, and mitoses. There is no invasion. At this time there may be no gross change, but the Schiller test with iodine may be positive and there may be atypical cells in the vaginal smear, especially if the glands are involved. Only eighteen examples of this lesion have been followed without treatment into the invasive stage of cancer (Younge, Hertig, and Armstrong). In the evaluation of any given lesion, precaution should be taken to exclude recognized epithelial anaplasia in the edge of an invasive carcinoma (Galvin and TeLinde).

Moderately Advanced Stage. As the neoplastic cells invade, a firm, slightly elevated

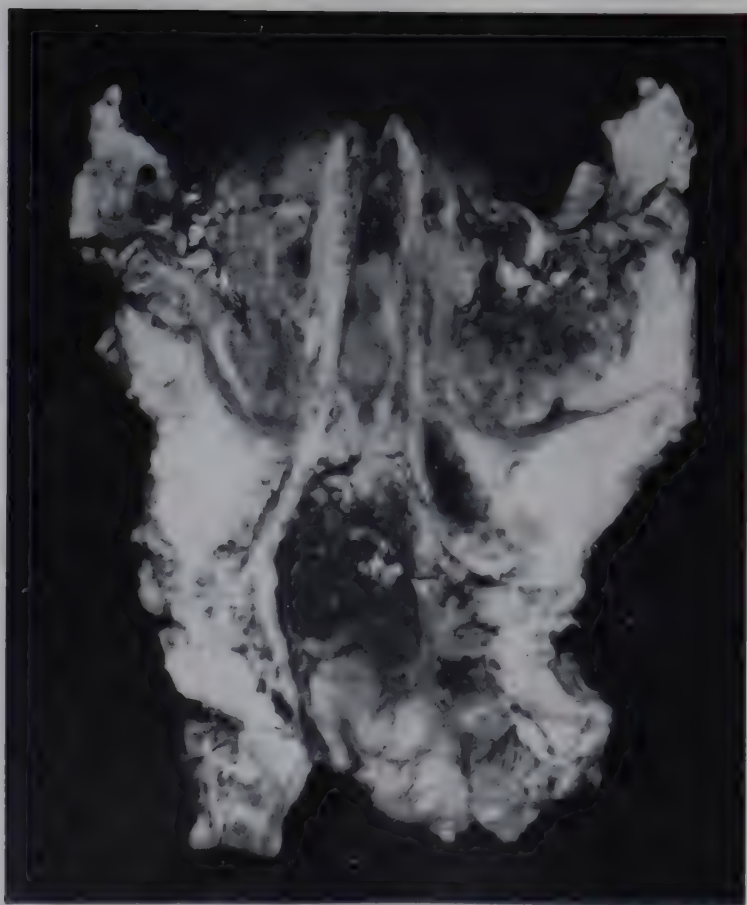


Fig. 438. Carcinoma of cervix.

nodule is formed. Soon there is ulceration, and an area up to a centimeter in diameter appears as a red granular focus which bleeds easily. Further growth proceeds in either of two ways: formation of a fungating, ulcerated, friable mass extending into the vagina, or an

Plaut). The relation of the grades to other factors is shown in Table 56, compiled from the figures given by Warren.

Advanced Stage. Regional Invasion. The neoplasm gradually replaces the cervix, and ulceration may result in complete destruction.

TABLE 56. CERVICAL CARCINOMA: RELATION OF GRADES TO OTHER FACTORS

	Epidermoid Carcinoma			Adeno- acanthoma	Adeno- carcinoma
	Grade I	Grade II	Grade III		
Average age at death	53 years, 7 months	51 years	45 years, 4 months	53 years, 3 months	57 years, 6 months
Average duration of disease . .	2 years, 9 months	2 years, 1 month	1 year, 2 months	2 years, 3 months	3 years, 6 months
Per cent visceral metastases at time of death	4	34	67	67	25

infiltrating tumor producing enlargement and induration of the entire cervix.

The microscopic appearance varies with the type. Grade I (spinous cell), Grade II (tran-

After penetration of the cervical wall, extension follows: laterally into the broad ligament, anteriorly into the base of the bladder, posteriorly into the uterosacral ligaments,

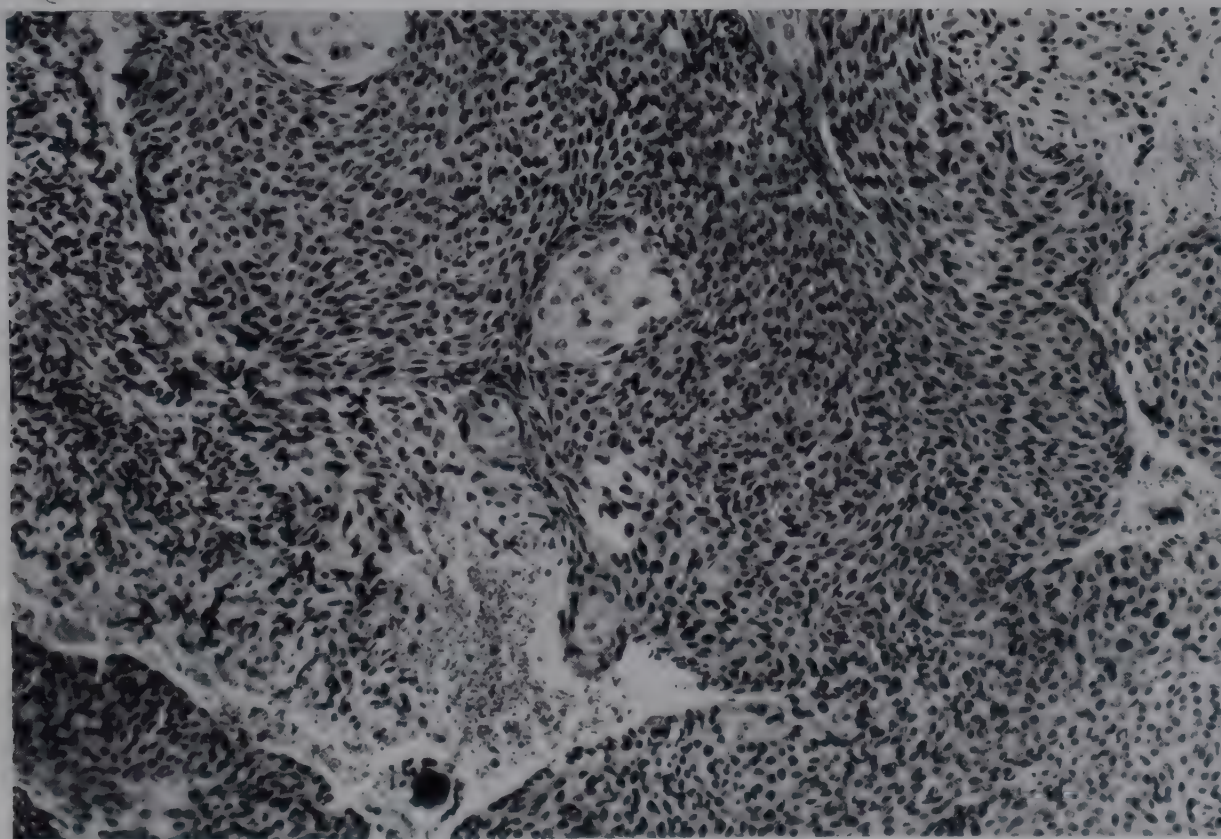


Fig. 439. Carcinoma of cervix. (Slide by courtesy of Dr. John Hobbs.)

sitional cell), and Grade III (spindle cell). The important points to consider in grading are the cell type, the degree of keratinization in the spinous cells, the number of mitoses, and the relation of tumor to stroma (Warren;

pelvic floor, and rectum, caudally to the vaginal wall, and cephalad to the fundus.

Metastases. Lymph drains from the cervix to small inconstant nodes in the broad ligament at the junction of the fundus and cervix

and in the vesicocervical septum. The most significant regional nodes are located where the lymph vessels cross the ureters and at the bifurcation of the common iliac arteries (Taylor and Nathanson; Taussig).

The incidence of nodal metastases varies with the stage of the disease. The grade of the tumor is also a factor, especially in the frequency of distant nodal metastases. Visceral metastases are commonest in the lungs and liver, with fewer in the peritoneum, adrenals, and bone (Warren).

Adenocarcinoma. This type presumably arises from the cervical glands and epithelium of the cervical canal. The gross appearance, invasion, and prognosis are essentially the same as for the epidermoid carcinoma. The cells are typically tall columnar and mucus-secreting, and are arranged in acini.

Adeno-acanthoma. Tumors composed of a mixture of squamous cells and columnar cells are seen in both the cervix and fundus. The prognosis is the same as in the other types, or is less favorable.

Incidence. Causal Factors. Age. The highest incidence of cervical carcinoma is in the fifth decade, but examples are seen in all decades, including the first.

Pregnancy. Over 90 per cent of all cervical carcinomas are in parous women and only 13 per cent in primiparas. In several series of cases, patients averaged between five and six children each. The significance of these facts cannot be definitely evaluated. That stimulation of the estrogenic hormones is a factor is borne out by the production of atypical hyperplasia of the cervix in animals by injection of estrogens and the appearance of reversible lesions similar to carcinoma in situ in pregnant women (Hellman). Clinical observations emphasize the importance of obstetric lacerations and the associated chronic inflammation as causal factors.

Leukoplakia of Cervix. Leukoplakia of the cervix occurs as single or multiple white foci, in which there is hyperkeratinization. A few carcinomas appear to arise in leukoplakia.

Carcinoma of the Cervical Stump. In about 1 per cent of patients who have had supra-cervical hysterectomy, carcinoma develops in the cervical stump. The clinical and anatomic features of the disease are the same as in the usual types, except that the five-year survival

rate is lower—14 per cent (Healy and Arneson).

Clinicopathologic Correlation. Ulceration of the tumor is responsible for the two cardinal signs, vaginal bleeding, and leukorrhea, in 60 per cent of patients. The bleeding may be menorrhagic or metrorrhagic or occur after intercourse. Other signs and symptoms directly related to the primary tumor are observed in only a few patients. Extension to and irritation of the bladder is the cause of frequency, nocturia, and dysuria, seen in about half of patients. Symptoms referable to the rectum are uncommon except for late fistulas. The loss of blood by vaginal bleeding rarely leads to severe anemia (Henriksen).

Prognosis. The average five-year survival is in excess of 50 per cent.

Cause of Death. In three-quarters of patients the carcinoma invades the pelvic tissue about the ureter and compresses it, and death is caused by urinary obstruction, urinary infection and uremia (Graves, Kickham, and Nathanson). The other quarter of patients die of a wide variety of causes.

Influence of Pregnancy. Pregnancy has an unfavorable influence on carcinoma of the cervix—the tumor grows more rapidly during pregnancy and the puerperium, and disseminates widely during the puerperium. The first effect is probably related to increased vascularity and the latter to the trauma of delivery (Danforth).

Complications of Treatment with Radiant Energy. The early complications are radiation proctitis and cystitis. Late complications include ulceration of and fistulas into the bladder and rectum, pyometria, rectal stricture, and pelvic or generalized peritonitis (Healy and Frazell). Lesions of the intestine are prone to occur if the intestinal loops are adherent in the pelvis.

Displacements of the Uterus

The uterus in most women is set at an angle of about 90 degrees with the vagina, and the fundus is angulated a further 45 degrees with the cervix; it is therefore anteverted and anteflexed normally.

Anteflexion. An abnormally acute anteflexion is usually developmental in origin, and is frequently associated with hypoplasia of the uterus.

Retrodisplacement and Retroflexion. A moderate degree of retroflexion occurs in many women and causes no symptoms. More advanced degrees may be associated with poor venous drainage and resultant hyperemia of the uterus. Symptoms are backache and bearing down.

Prolapse. Prolapse, or uterine descensus, is a low position of the uterus, in the extreme degree of which the entire organ projects through the vaginal orifice—procidentia. The

which may be easily recognized: proliferative, secretory, and bleeding. During the first half of the cycle under the influence of estrogen, the epithelium gradually increases in height and the glands become convoluted. With the appearance of lutein cells glycogen appears in the basal part of the epithelial cell. As the secretory phase progresses the vacuoles of glycogen move to the luminal wall and rupture into the lumen. At the same time the stromal cells become larger and resemble decidual

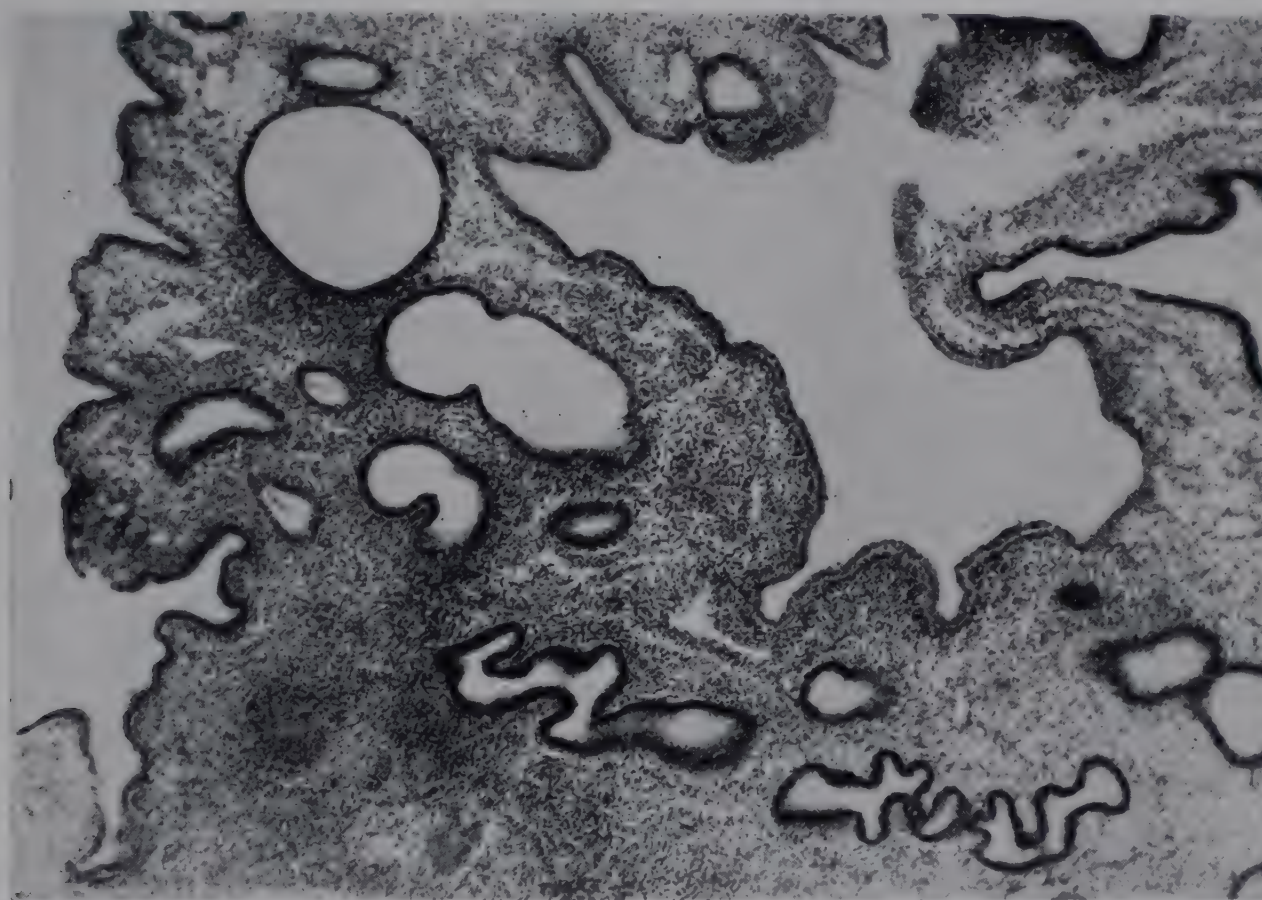


Fig. 440. Hyperplasia of endometrium. (Slide by courtesy of Dr. John Hobbs.)

vaginal mucosa covers the projecting mass, and a part of the bladder is pulled downward beneath the covering of the sac. Angulation of the ureters and hydronephrosis may follow (Lieberthal and Frankenthal). Similarly on the posterior side the rectum is pulled outward. The vaginal mucosa becomes thickened and indurated. The usual cause of prolapse is relaxation of the broad and uterosacral ligaments incident to the injuries of childbirth.

The Relation of the Endometrium to Hormonal Control

Anatomic Types of Endometrium. For detailed description of the appearance of the endometrium during the normal cycle special texts should be consulted. There are three general types of physiologic endometrium

cells. There are edema of the stroma and infiltration with leukocytes. The spiral arteries are prominent. The bleeding phase is characterized early by degeneration in the luminal cells and later by desquamation of the greater part of the endometrium associated with hemorrhage.

There are two important deviations from this cycle—anovulatory endometrium and hyperplasia.

The endometrium in an *anovulatory cycle* shows the proliferative changes, but poorly developed secretory changes. It is probably related to a deficient formation of the corpus luteum.

Hyperplasia is the response of the endometrium to continued estrogenic stimulation incident to persistence of graafian follicles and failure of ovulation and of formation of a

corpus luteum. The endometrium is usually thicker than normal, and frequently thrown into redundant masses appearing as polyps—hence the older name of “polypoid endometritis.” The tissue is firm and the surface intact. The hyperplasia involves an increase of both epithelium and stroma. The epithelial cells of the surface and of the glands are tall columnar, and mitoses are seen. The glands vary in size from small acini to large cystic spaces. The stromal cells are abundant, and many are in mitosis. Throughout are small foci of necrosis, at times associated with thrombi in the vessels, which some regard as the source of the bleeding (Novak and Martzloff). Rarer variants include conspicuous hyperplasia of epithelium or stroma (suggesting a malignant tumor) and focal squamous metaplasia.

Postmenopausal Hyperplasia. Hyperplasia of the endometrium is occasionally seen after the menopause and may be a forerunner of carcinoma (Novak and Yui).

Functional Uterine Bleeding

This is that type of uterine bleeding in which there is no demonstrable gross anatomic change in the genital organs.

Pathologic Anatomy. There is in general a correlation between the anatomic structure of the endometrium and functional bleeding. Thus, in the careful study of biopsies made by Hamblen, all varieties of hormonal effect were observed:

Type of Response	Per Cent
Hypo-estrogenic	13.9
Normal estrogenic	2.0
Progestational	11.0
Estrogenic with focal progestational . . .	12.9
Persistent estrogenic	34.5
Hyperestrogenic	25.6

Inflammations of the Uterine Fundus

Specific inflammations of the endometrium are caused by gonococci and tubercle bacilli. Puerperal metritis has been discussed in another chapter (p. 274).

Chronic Endometritis. There is no agreement among clinicians or pathologists on the nature of what is called “chronic endometritis.”

Pathologic Anatomy. In sections, infiltra-

tions with lymphocytes and plasma cells, proliferation of fibroblasts, and deformation of glands are seen. Only rarely are there exudative cells within the glands.

Causal Factors. This type of interstitial inflammation is seen in the endometrium over a submucosal leiomyoma, in association with atrophy in postmenstrual women, and in post-abortal states with retention of placental remnants. There are also examples which are apparently primary.

Types of Lesions of the Myometrium. There are three distinctive lesions of the myometrium, characterized anatomically by diffuse symmetrical enlargement of the uterus, and clinically by bleeding, menorrhagia, leukorrhea, and pelvic discomfort. They are chronic subinvolution, chronic metritis, and hypertrophy (Schwarz). In all there is frequently hyperplasia of the endometrium, indicative of a hormonal imbalance.

Chronic Subinvolution. The uterine wall is thickened, and the blood vessels are prominent. Perivascularly and between the muscle bundles, there are excessive elastic fibrillae. The muscle fibers are enlarged, and there are hyalinization of the connective tissue and interstitial edema.

Chronic subinvolution is seen only in parous women, and represents inadequate puerperal involution.

Chronic Metritis. In this type there are an increase of fibrous tissue and infiltration of lymphocytes, but the characteristic elastic tissue of subinvolution is lacking. It is observed in nulliparous or parous women, and in three-fourths there is a concomitant tubal inflammation.

Hypertrophy. The enlargement of the uterus is caused entirely by hypertrophy of muscle. There are no changes in the interstitium or blood vessels.

Endometrial Polyp

The endometrial polyp, as distinguished from polypoid hyperplasia of the endometrium, is a single or multiple, sessile or pedunculated neoplasm. It is composed of the epithelial and stromal elements of the endometrium. In some, both types of cells show the changes of the menstrual cycle, and the general appearance is that of the corporal endometrium of the same uterus. Others do not

follow the cyclic changes, but show hyperplasia. The acini vary in size, and the lining cells are cylindrical or cuboidal.

The cause is unknown, but repeated focal hyperplasia with failure of involution, as has been postulated for nodular hyperplasia of the thyroid, may be the pathogenesis.

Endometriosis

Endometriosis is an ectopic focus of epithelium derived from the müllerian duct. It is

network and is connected with the endometrium, indicating that the lesion originates by invasion (Cullen).

The tumorlike nodule may be composed of epithelium and stroma-endometrioma or muscle-adenomyoma. Nodules are commonest in the uterine cornua (Cullen).

Clinicopathologic Correlation. Uterine endometriosis is a disease of women between twenty-five and fifty years of age, occurring without regard for parity. The clinical observations are inconstant, and are related to en-

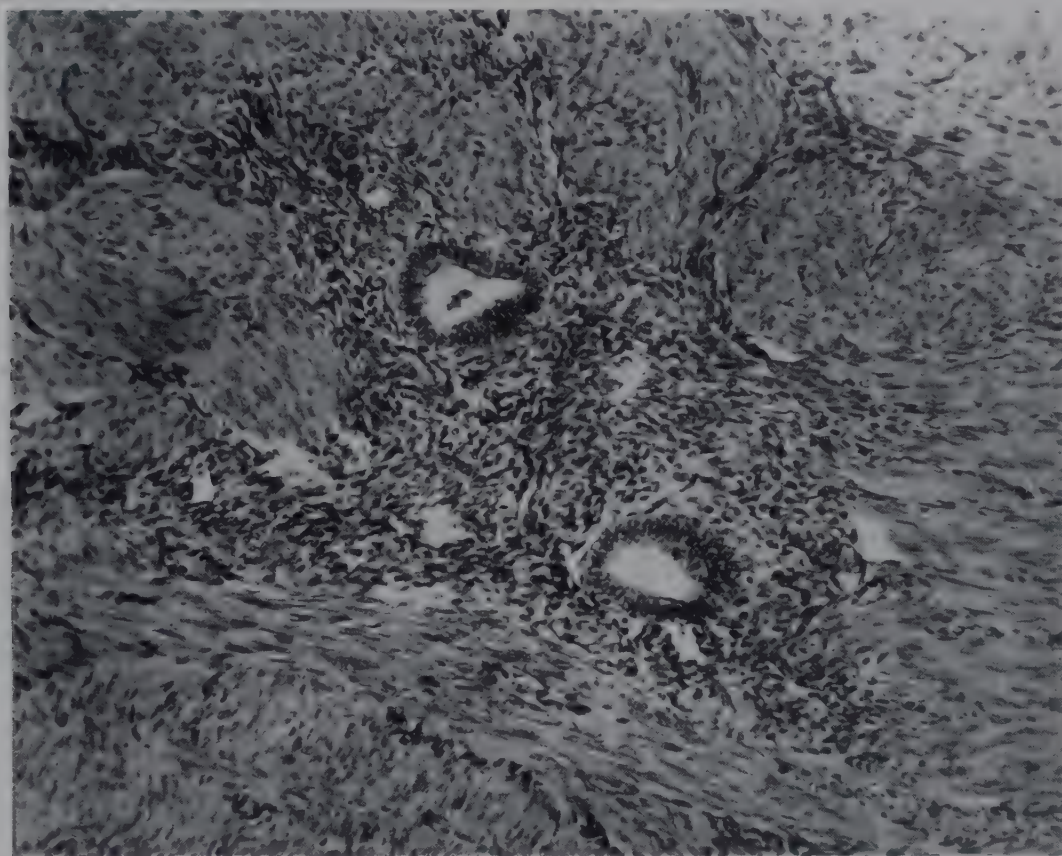


Fig. 441. Endometriosis of uterine wall.

convenient for description and analysis to recognize two types: intra-uterine and extra-uterine.

Intra-uterine Endometriosis (Adenomyosis, Adenomyoma). The endometriumlike glands may be diffusely distributed throughout the myometrium or collected into small or large nodules.

Pathologic Anatomy. In diffuse adenomyosis the uterus is enlarged, and the cut section appears as an interwoven mass of fibrillary tissue, similar to the gross appearance in chronic subinvolution. The epithelial islands are surrounded by a small amount of endometrial stroma. The cells are tall columnar, and in general show the usual cyclic changes. Recent and old hemorrhage is frequently demonstrable. With serial sections it can be shown that all the ectopic tissue forms a continuous

largement of the uterus and to menstrual disturbances.

Extra-uterine Endometriosis. *Pathologic Anatomy.* Endometriosis appears as a black or brown cystic nodule, most frequently on the undersurface of the ovary, the proximal part of the broad ligament, and posterior surface of the cervix. The nodules vary in size from less than a millimeter to several centimeters. The larger cysts rupture, and secondary nodules and peritoneal adhesions result (Sampson).

The typical epithelium may or may not be enclosed in endometrial stroma, and the response to hormones is dependent on the exact origin. The epithelial cells may be similar to those of the endometrium or of the tube. The presence of hemorrhage and of phagocytes with hemosiderin in the stroma is the rule.

Occasionally, a decidual reaction in the stroma may be observed.

Less common locations are the serosal surface of the intestine (Jenkinson and Brown), the abdominal wall especially about the umbilicus and about surgical wounds, the wall of the bladder (Kahle, Vickery, and Maltry), the vagina, the vulva, the rectovaginal septum (Masson), the pelvic lymph nodes (Javert), and the lung (Hobbs and Bortnick).

Pathogenesis. Numerous theories have been proposed to explain the presence of ectopic endometrium. Transport by expulsion through the tube during menstruation, by lymphatics or veins, and artificially during a surgical procedure (Jacobson), is probably the usual mechanism.

This is supported by the production of endometriosis in monkeys by directing the menstrual flow into the peritoneal cavity.

Clinicopathologic Correlation. The clinical picture of endometriosis results from the presence of a nodule of tissue responsive to the ovarian hormones: swelling and hemorrhage coincident with the bleeding of menstruation. In the deeper tissues, such as the ovary, the manifestation is only pain; in the superficial tissues, such as the abdomen or vulva, there is in addition blue discoloration; and in the hollow viscera, such as the bladder, bleeding.

Sterility and menstrual disorders are common. The symptoms are observed only in sexually adult women, since there is atrophy of the tissues of endometriosis after the menopause. Endometrial carcinoma is more common in women with endometriosis (Javert).

Leiomyoma of the Uterus

Leiomyoma of the uterus, designated incorrectly as "fibromyoma" and colloquially as "fibroid," is the commonest tumor in human beings.

Pathologic Anatomy. Leiomyoma is first recognizable as a tiny, firm, spherical white nodule, 1 mm. or less in diameter, in the wall of the uterus. As seen on the cut section it bulges from the surface and can be easily shelled out, leaving a smooth wall of fibrous tissue and compressed uterine muscle. Continued growth is slow, and it is estimated that several years elapse before the nodules reach palpable size.

The usual picture is one of multiple, spheri-

cal, firm nodules in all parts of the uterus, frequently deforming the wall and cavity. Each nodule is composed of an interlacing network of white, fibrillar, shining tissue—the "watered-silk" appearance. There is a definite capsule of fibrous tissue. Tumors may project into the uterine cavity, and are then designated as "submucous" myomas. Occasionally, they become pedunculated, and project through the cervix or vulva. Other tumors project into the peritoneal cavity, and are called "subperitoneal" or "subserous" myomas. Nodules in the wall of the fundus are known as "intramural" myomas, and in the cervix as "cervical" myomas. It seems probable that all locations except the fundal myometrium are secondary, and represent the forcing of the myoma out of the wall by uterine contractions.

The structure of the myoma is an intertwining network of bundles of spindle-shaped cells with ovoid vesicular nuclei. In smaller myomas there is little interstitial fibrous tissue, but in larger tumors the fibrous tissue is conspicuous, and may even be more abundant than the muscle.

Secondary Changes. As the myomas grow to larger size, there is restriction of blood supply, and numerous secondary changes occur. The fibrous tissue and muscle may undergo hyaline change and fuse to a homogeneous, acidophilic mass. Hemorrhage and necrosis are common, and foci may soften to form cystic spaces filled with limpid or viscid fluid. Calcification in foci of hyalination and necrosis is a frequent secondary change. All secondary changes are conspicuous during pregnancy, partly because of pressure, and partly from hormonal stimulation of the muscle cells.

Incidence. Causal Factors. Age. Leiomyomas are rarely seen before the twentieth year of life, and reach a peak incidence in the later years of sexual life, between thirty-five and forty-five.

Race. Corrected statistics show that leiomyomas are three times as common in colored as in white women (Torpin, Pund, and Peebles). In routine autopsies of women more than twenty years of age, leiomyomas are found in about 30 per cent of the colored race and 10 per cent of the white race.

Anomaly of Uterus. The close association of small myomas with blood vessels, and the

observation of anomalies and heterotopic tissue in uteruses with myomas, have suggested to some that an anomaly in the formation of blood vessels is a causative factor (Ewing).

Hormones. Associated Lesions in the Uterus and Adnexa. Although the reported incidence of associated lesions varies, investigators agree that hyperplasia of the endometrium, polyps of the endometrium, and adenomyosis of the uterus are commoner in patients with than without myomas. From this fact it is concluded that these four lesions have some common causal factor, probably hyperestrinism, but that each is based also on other as yet unknown causal factors (Light). Some support for this view is given by the experimental production of peritoneal fibromyomas in guinea pigs by injection of estrogens, and prevention of the change by simultaneous injection of androgens or progesterone (Lip-schütz).

Further evidence that estrogen plays a role comes from the observation that myomas apparently grow more rapidly during pregnancy (Charlewood), and sometimes decrease in size after the menopause. An association of myoma with carcinoma of the endometrium has also been noted (Wharton).

Physiologic Aspects. The muscle in a leiomyoma is capable of contraction, and responds to stimulation with pituitrin, histamine, and ergot as does uterine muscle (Bryan and Warren).

Extra-uterine Leiomyoma. Similar tumors are seen in the broad ligament, round ligament, vagina (Bennett and Ehrlich), uterine part of the tube, and in the pelvic fascia.

Sarcomatous Change. In a significant number of myomas (probably about 1 per cent), small or large foci of sarcoma are observed, especially in the submucous type. Sarcoma is to be recognized as a soft, fleshy, reddish gray or yellow, friable tissue within a myoma or completely replacing a nodule. Most are leiomyosarcomas, but fibrosarcoma is observed. The presence of tumor giant cells in a myoma is regarded by some as a criterion of rapid growth and malignant change (Mallory and Stewart).

Clinicopathologic Correlation. Most myomas of the uterus are asymptomatic. When signs and symptoms are present, they result from the physical presence of the tumor, from distortion of the uterus, from pressure on and

adherence to surrounding structures, and from secondary changes in the myoma.

Myomas of the usual size are readily palpable by bimanual examination. As the tumors enlarge, the uterus is distorted and elevated out of the pelvis so that the bladder is pulled upward. The uterus under these conditions is not a satisfactory tissue for implantation, and most women with myomas are sterile. That



Fig. 442. Leiomyoma of uterus.

the myoma is the cause of the sterility and not an effect is shown by the observation that about a third of such sterile women become pregnant after myomectomy. The same disturbance is probably responsible for menorrhagia—one of the common symptoms.

As the uterus enlarges, the surface is brought in contact with other structures. Not infrequently adhesions form between the myoma and the intestine or abdominal wall. If the myoma is pedunculated, the pedicle may disappear, and the tumor is then attached only to another organ—a parasitic myoma. Submucous myomas may by downward pull cause

inversion of the uterus. Pressure on the bladder, ureters, and intestine is often present, but does not lead to prominent symptoms. Subserous myomas may twist on the pedicle and cause sharp pain. Pain is also caused by deformity of the uterine cavity and accumulation of blood and secretion behind a point of stenosis. The feeling of a weight in the abdomen and backache are probably related to the actual weight of the mass in the pelvis.

Carcinoma of the Endometrium

Carcinoma, usually adenocarcinoma, of the endometrium (uterine fundus) is a less in-

The Polypoid Type. As the name indicates, this type is a single polyp or a confluent polypoid mass. In both the circumscribed and polypoid types, invasion of the myometrium is evident as an irregular line of demarcation or as yellow-gray foci in the muscle.

Adenocarcinoma and Adeno-acanthoma. Most carcinomas are of Grades I and II, and are adenocarcinomas. The cells are tall columnar, with basal or central vesicular nuclei and definite cell boundaries (Elton). The stroma is ordinarily loose and well vascularized. Adeno-acanthoma, similar to that in the cervix, is also seen in the fundus.

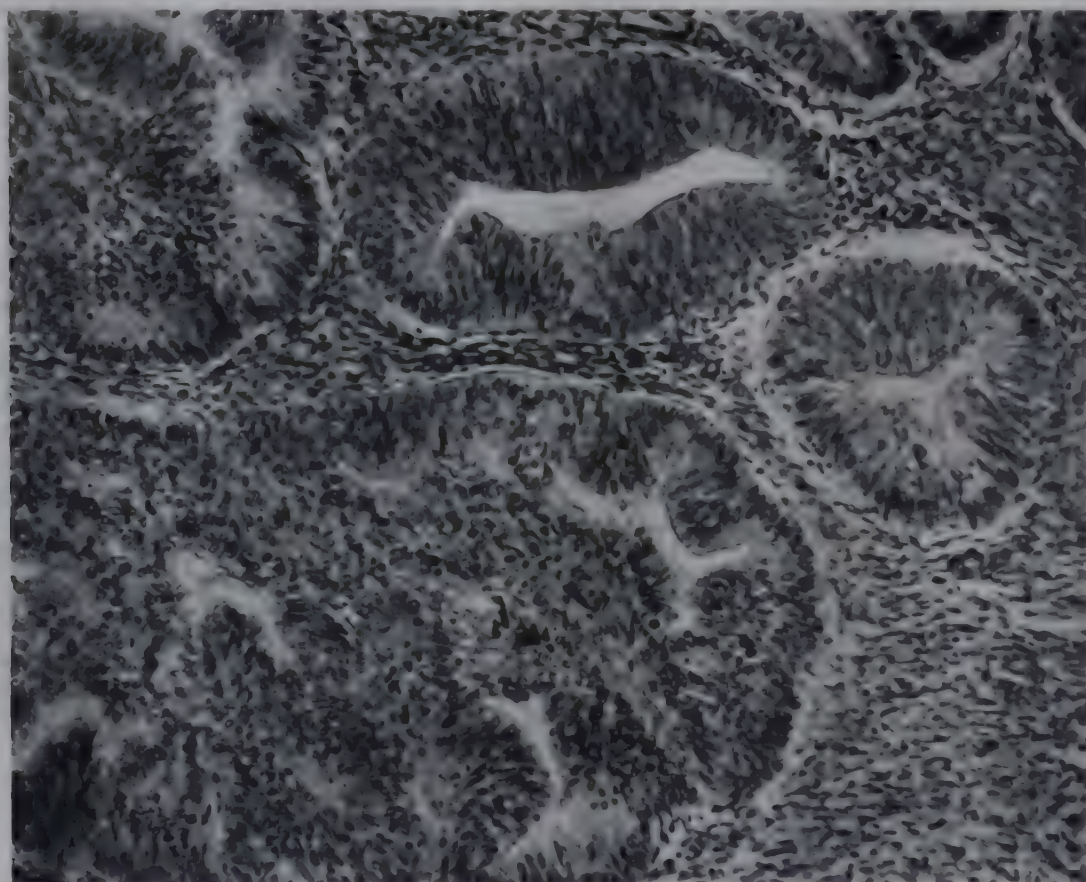


Fig. 443. Carcinoma of endometrium.

vasive and more slowly growing neoplasm than epidermoid carcinoma of the cervix.

Pathologic Anatomy. As seen in surgical and postmortem specimens, carcinoma of the endometrium may be diffuse, circumscribed, or polypoid.

The Diffuse Type. In this type, all or the greater part of the endometrium is replaced by a soft, friable, granular tissue, varying from 5 to 10 mm. in thickness. The line of demarcation from the myometrium may be distinct, or the neoplastic tissue may extend into the wall at one or more points.

The Circumscribed Type. This type is a focal tumor, usually in the extreme fundus. It extends into the lumen as a solid or papillary mass, frequently irregular and ulcerated.

Course. With continued growth the carcinoma penetrates the wall of the uterus and spreads into the broad ligaments.

Incidence. Causal Factors. Age. Carcinoma of the endometrium is largely a disease of women in the fifth, sixth, and seventh decades of life, with an average age of about fifty-eight years. Approximately 70 per cent have passed the menopause.

Parity. Of the 730 patients observed at the Mayo Clinic in twenty-four years, 10 per cent were single, 26 per cent were married nulliparas, 16 per cent were primiparas, and 48 per cent were multiparas (Masson and Gregg).

Other Tumors. Association of carcinoma of the endometrium with other tumors of the

uterus, sarcoma of the uterus, and carcinoma of the cervix is not in excess of what might be expected by chance. Carcinoma developing in a preexisting endometrial polyp has been observed.

Cirrhosis of Liver. Speert has called attention to the association of endometrial carcinoma and cirrhosis as evidence of abnormal and persistent estrogenic stimulation as a causal factor.

terectomy averages 60 per cent with values of 75 per cent in Grade I tumors and 40 per cent in Grade IV tumors (Masson and Gregg).

Vaginal Smear in Uterine Carcinoma. In carcinoma of both the cervix and endometrium, the superficial cells of the tumor are shed and may be seen in a smear of the vaginal content if properly prepared. By study and experience, considerable skill in diag-

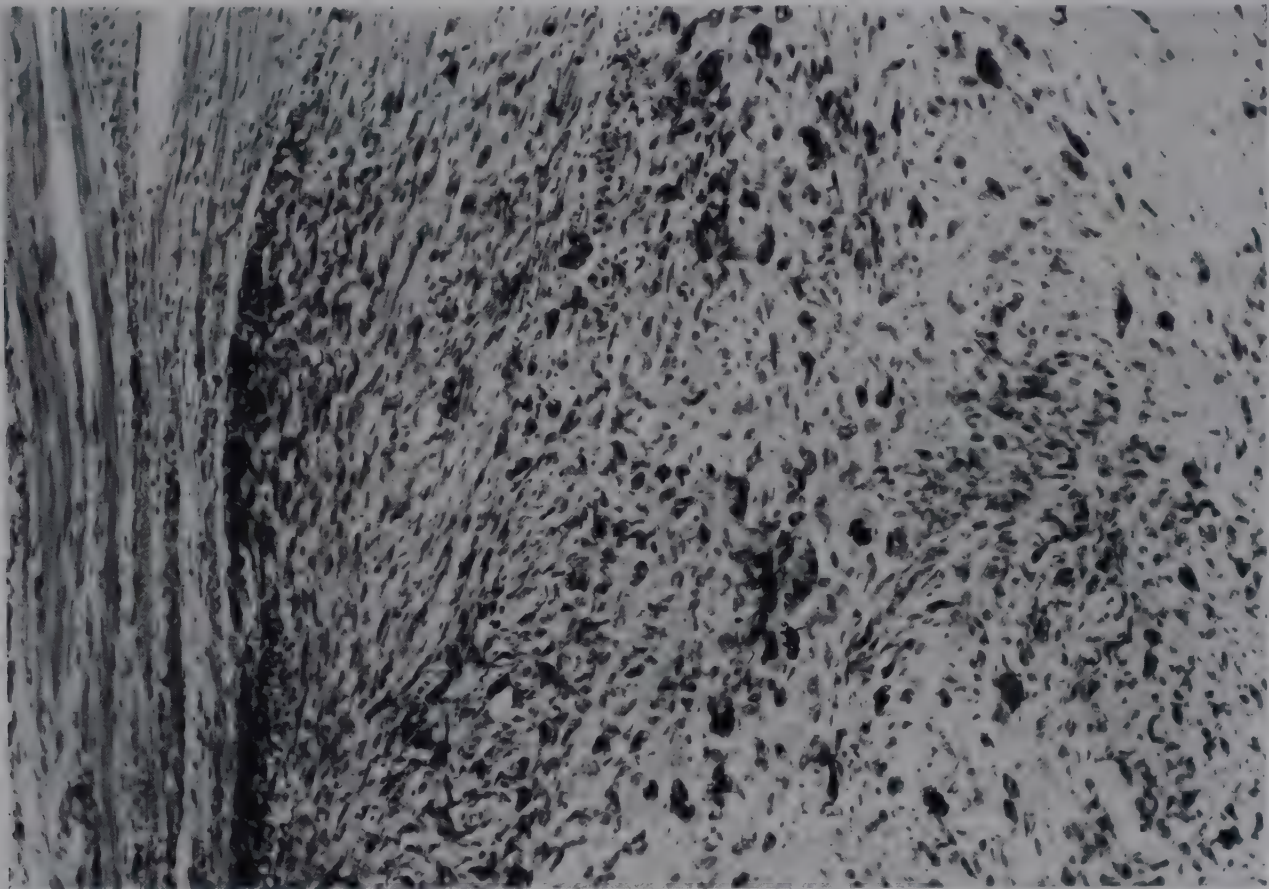


Fig. 444. Leiomyosarcoma of the uterus.

Endometrial Hyperplasia. About one-quarter of endometrial carcinoma occurs in a postmenopausal hyperplasia of the endometrium.

Menstruation. Menopausal Age. There are no unusual features in the menstrual history of patients with carcinoma of the endometrium, but the menopausal age is, according to some studies, greater than in women who presumably do not develop uterine carcinoma (Crossen and Hobbs).

Clinicopathologic Correlation. Ulceration and hemorrhage from the tumor are the causes of the two commonest signs: vaginal bleeding and abnormal vaginal discharge. The loss of blood is usually not excessive, and extreme degrees of anemia are only rarely seen.

The slow growth of most tumors is indicated by the long interval before consultation with a physician is sought—a year to a year and a half. The five-year survival rate after hys-

terectomy averages 60 per cent with values of 75 per cent in Grade I tumors and 40 per cent in Grade IV tumors (Masson and Gregg).

Sarcoma of the Uterus

Sarcoma comprises about 5 per cent of all malignant tumors of the uterus (Novak and Anderson). The five-year survival rate does not exceed 30 per cent.

Types. Four types are recognized: sarcoma arising in a myoma, sarcoma of the myometrium, sarcoma of the endometrium, and botryoid sarcoma. The first is discussed in the section on myoma of the uterus (p. 909).

Myometrial Sarcoma. Primary sarcoma of the uterine wall may appear as a circumscribed nodule or as a diffuse enlargement of the entire fundus. In the former instance it is difficult to determine whether or not there was a preceding myoma. Most are leiomyomas.

Endometrial Sarcoma. Most sarcomas of the endometrium are polypoid and of the spindle cell type.

Botryoid Sarcoma. In the cervix and less commonly in the fundus of both adults and children, a characteristic tumor may be observed, composed of a confluent polypoid mass of pink, soft, edematous tissue. In addition to spindle cells, striated muscle cells and islands of cartilage are seen. It has been suggested that these tumors are teratomas, that they are derived from fetal tissue left in the uterus after delivery, and that they are true mixed tumors (Lebowich and Ehrlich).

Tumors of the Uterine Tube

Primary carcinoma of the salpinx constitutes about 0.5 per cent of all malignant tumors of the pelvic female genital tract. The frequently associated salpingitis may be an effect and not a cause of the carcinoma. The usual type is adenocarcinoma in papillary or solid arrangement. Other primary tumors are rare. Metastatic tumors usually originate from other pelvic viscera (Finn and Javert)

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CIII

Diseases of the Breast

The breast is a modified skin appendage composed of three distinctive types of epithelium and at least two distinctive types of connective tissue. The tissues of the breast are under hormonal control. Although our knowledge is incomplete, it seems likely that the hormones of the pituitary gland and of the ovary play a role in the causation of most lesions of the breast.

Congenital Anomalies of the Breast

Agenesis, aplasia, and hypoplasia have been reported. In most instances the lesion is bilateral. The most common anomaly of the breast is polymastia. Accessory nipples and primitive lobules of breast tissue may be found anywhere along the milk lines of mammals. They are most common in the axilla and may escape attention until there is hyperplasia during a pregnancy.

Hypertrophy of the Female Breast

Three general types of hypertrophy of the female breast are recognized, infantile, puberal, and adult. Infantile hypertrophy is usually associated with precocious sexual development. In puberal hypertrophy the usual enlargement of the breasts at this age continues either in one or both breasts until after four or five years the breasts are from two to five times normal size. The association with some disturbance in the sex hormones is not clear, but most patients give a history of menstrual irregularity. Hypertrophy of the breast in adults is rare, and in most instances is associated with functional tumors or carcinoma of the ovary.

Gynecomastia

Gynecomastia is an enlargement of the male breast. It is associated with injury to the

breast, injury and atrophy of the testes, and teratomas of the testes, and occurs in puberal boys and older men. There is also some evidence of a familial influence. There is proliferation of both connective tissue and ducts, the latter more frequently by elongation rather than budding (Karsner).

Gynecomastia has followed the use of estrogenic hormones in men, and androgens have been used successfully in the treatment of some young men with gynecomastia. In puberal boys there is an associated abnormal urinary excretion of 17-ketosteroids (Nathanson).

Proliferative and Cystic Lesions of the Breast

The interrelations of the proliferative and cystic lesions of the breast and their relation to carcinoma are most confused and the subject is controversial. As each lesion has been described a new name has been proposed, so that today there are numerous synonyms. The best approach with our present knowledge is to think in terms of lesions rather than of disease entities. Foote and Stewart recognize lobular atrophy, cyst formation, duct papillomatosis, blunt duct adenosis, hyperplasia of apocrine epithelium, sclerosing adenosis, periductal mastitis, and alterations in lobular pattern.

Lobular Atrophy. A decrease in the size of the lobules and a decrease of the number of lobules becomes more frequent with increasing age and is observed in about one-fourth of all proliferative and cystic disease of the breast.

Cyst Formation. Grossly visible cysts, that is, cysts over 1 mm. in diameter, are present in one-half of all noncancerous disease of the breast. The lining epithelium rarely shows hyperplasia, but there is frequently associated duct hyperplasia and papillomatosis.

Duct Papillomatosis. Papillomatosis in the large and small ducts, partially or totally occluding them, occurs in about a fourth of patients without associated cancer. The epithelium is not atypical and shows no invasion.

Blunt Duct Adenosis. This lesion is usually seen in the distal extremities of the ducts. Early there are ducts not arranged in lobular pattern, with proliferation of the epithelium and condensation of surrounding elastica. Late there is dilatation and flattening of the epithelium. It is observed in one-fourth of all noncancerous breast lesions.

Hyperplasia of Apocrine Epithelium. Apocrine epithelium is recognized grossly as yellowish brown, elevated, glistening foci, and microscopically as tall cylindrical cells with small nuclei and abundant eosinophilic cytoplasm. The foci may be isolated or connected with the ducts and are present in one half of noncancerous breast lesions.

Sclerosing Adenosis. This lesion, especially when it occurs as a nodule, is likely to be confused with carcinoma by both the clinician and pathologist. The highest age incidence is in the twenties and thirties. Grossly the nodules are movable in the breast, are moderately firm, are indefinitely encapsulated, and are composed of nodules varying from a millimeter to a centimeter in diameter. The essential change is a fibrosis and hyalinization which isolates the epithelium in an irregular pattern, suggestive of carcinoma, especially in frozen sections.

Similar lesions may be observed microscopically when there is no grossly detectable nodule; in fact this lesion is far more common than the palpable tumor, and is present in one-eighth of noncancerous lesions of the breast.

Periductal Mastitis. Infiltration of lymphocytes in the periductal tissue is usually associated with atrophy of periductal myoid tissue, dilatation of ducts, and flattening of the epithelium. Fatty macrophages may be present in the lumen. In late stages there is loss of epithelium with severe inflammation and fat necrosis in the surrounding stroma. Lesions of this type are observed in one-fifth of noncancerous breasts.

Lobular Pattern. Diffuse or focal alterations of the lobules with edema or fibrosis of the stroma and atrophy or hyperplasia of the

epithelium are common in noncancerous breast lesions.

Causal Factors. With the present knowledge it may be concluded only that the proliferative and cystic lesions of the breast are related to abnormal hormonal stimulation, especially by alternate stimulation and involution (Taylor).

Relation to Carcinoma. In general carcinoma occurs more frequently in breasts with proliferative and cystic lesions than in normal breasts, especially in the younger age groups (Warren). The association with duct papillomatosis is more apparent than that with other lesions, and there is no observable association with atrophy, cyst formation, or sclerosing adenosis.

Clinicopathologic Correlation. The signs and symptoms will vary with the combination of lesions present in a given patient. Pain is probably related to dilatation of the ducts and inflammation. Cysts may be large and observed through the thin skin. Lumpiness is dependent on changes in lobular pattern, atrophy, and adenosis. Bloody discharge from the nipple is indicative of duct papillomatosis.

Tumors of the Ducts of the Breast

Tumors of the ducts of the breast are characteristically papillary, and may be benign or malignant. In either case there is bleeding from the nipple, especially following trauma. The benign types are more frequent between the ages of twenty and thirty-five, while the malignant forms are more common after thirty-five.

Papilloma. Intraductal papillomas are usually multiple. They vary from 1 to 2 cm. in diameter, are yellow and translucent, and have a fine, velvety surface. The dilated ducts are filled with a thin, serosanguineous fluid. Three histologic types are recognized: fibrous, glandular, and transitional. In the first there is a preponderance of connective tissue stalks, covered by a single layer of epithelium. Fusion of the stalks produces a pseudoglandular architecture. The glandular type is apparently formed by a subepithelial adenoma, projecting into the duct. In the third type the papillae are enclosed in transitional epithelium, and although benign, they recur frequently (Saphir and Parker). The true papilloma of the ducts should be distinguished from intraductal hy-

perplasia in cystic and proliferative lesions of the breast.

Papillary Carcinoma. The papillary carcinoma invades the wall of the cyst or duct and metastasizes early to the regional nodes. There is little evidence that the papillary carcinoma is derived from a preexisting papilloma (Hart).

Epidermoid Carcinoma. Malignant tumors of squamous cells originating by metaplasia or prosoplasia of the ductal epithelium constitute

Fibro-adenoma of the Breast

Fibro-adenoma is the most common benign tumor of the breast. It is a firm, elastic, circumscribed and encapsulated, spherical or lobulated mass, which on section is seen to be composed of a bluish gray or gray translucent tissue. Narrow interlacing slits may be discernible on the cut surface.

Pathologic Anatomy. Two microscopic types have been recognized: an intracanal-

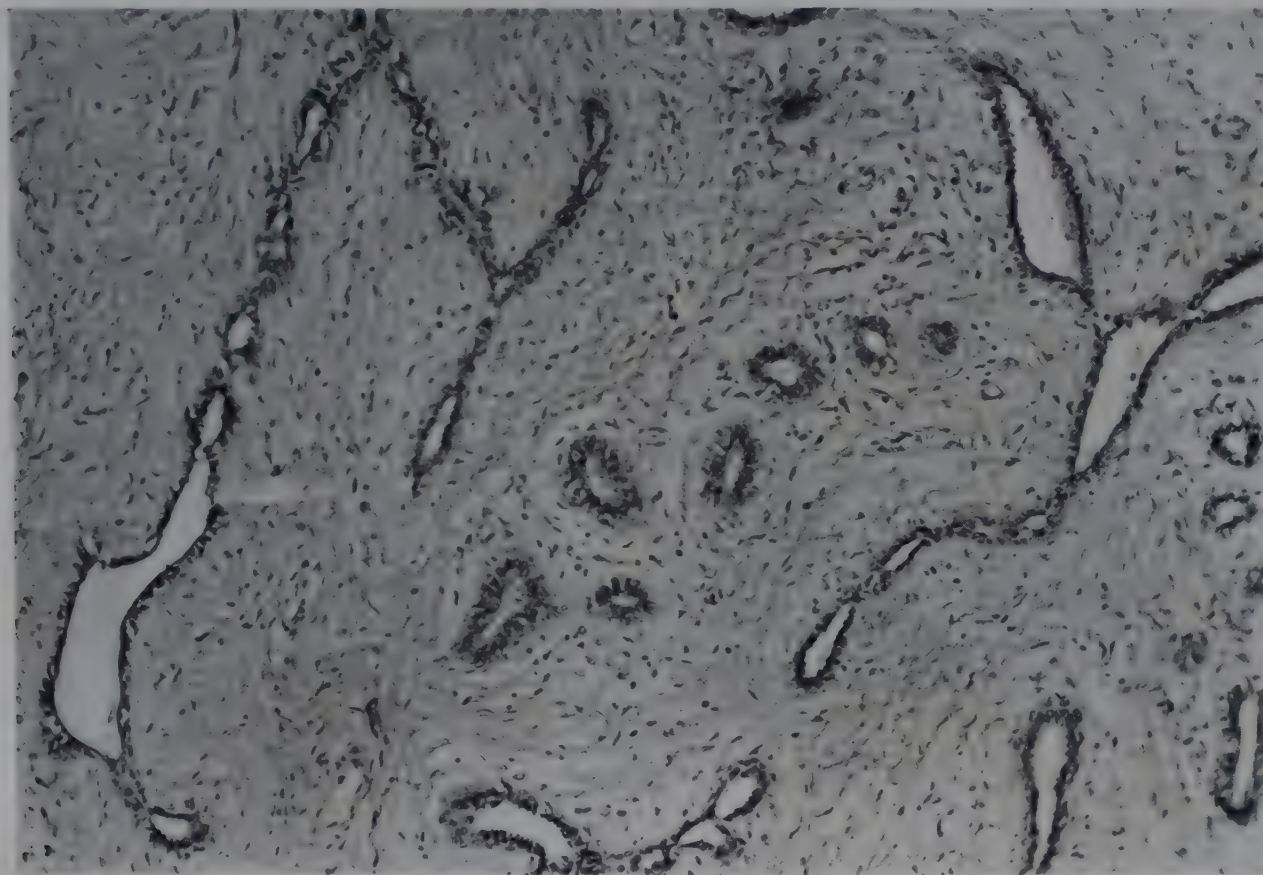


Fig. 445. Fibro-adenoma of breast.

less than 1 per cent of all carcinomas of the breast. They metastasize early and widely. Some apparently arise in a cystic and proliferative lesion (Foot and Moore).

Comedocarcinoma. The characteristic feature of the comedocarcinoma is that inspissated secretion can be expressed from the cut surface, and that the glands are filled with a dense, acidophilic, non-nucleated debris. It is thought by some that the comedocarcinoma is one of the less malignant types of carcinoma of the breast.

Mucinous Carcinoma. The true mucinous carcinoma of the breast is a rare type and relatively benign. There are dilated ducts and cysts filled with mucin and isolated neoplastic cells. In contrast is the signet ring cell mucinous carcinoma that is highly malignant, invades the breast extensively, and metastasizes widely (Saphir).

icular and a pericanalicular or periductal. Since in any one fibro-adenoma both types are encountered, little is gained by qualifying the diagnosis. The intracanalicular variety is made up of narrow branching spaces, lined by a single layer of cuboidal epithelium. The connective tissue is loose, and the individual cells are spindle-shaped or stellate, and are separated from one another by a lightly basophilic granular or stringy mucoid type of intercellular substance. In the periductal variety there is no deformity of the epithelial structures. The ducts are round and are lined by one or two layers of cuboidal or columnar cells. Concentrically around the lumen there is a denser connective tissue, with a moderate amount of collagen.

Incidence and Causal Factors. The typical woman with a fibro-adenoma of the breast is twenty to thirty-five years old and is unmar-

ried. If she has had children she has not nursed them successfully. She has a history of irregular menses, complains of dysmenorrhea and premenstrual pain in the breast, has an enlarged thyroid, has small breasts with small erect nipples, and is slender and underweight. These observations, to which there are of course exceptions, suggest that the woman with fibro-adenoma is sexually underdeveloped and has some basic disturbance of the ovarian hormones.

stitutes about 90 per cent of all tumors of the breast, 15 per cent of all malignant tumors in human beings and 30 per cent of all cancer in women (Pack and LeFevre).

Pathologic Anatomy. Careful macroscopic examination of the breast is of the greatest importance, especially in the detection of small foci of malignant transformation in chronic cystic mastitis and other diseases. In primary mammary carcinoma there is typically a single, extremely firm, nonelastic nodule, which has



Fig. 446. Carcinoma of breast. Note wrinkling of skin, smallness of breast, and retraction of nipple. (Photograph from the files of the Barnard Free Skin and Cancer Hospital.)

Malignant Change. Both carcinoma and sarcoma presumably originating in a fibro-adenoma have been reported. Most are of a low grade of malignancy and the prognosis is good (Harrington and Miller).

Clinicopathologic Correlation. The highest incidence of fibro-adenoma is between the ages of twenty and thirty-five. Most of the tumors at the time of first observation are from 1 to 5 cm. in diameter. The rate of growth is irregular, and usually is more rapid during the first few months. It is said that they increase and decrease in size with each menstrual cycle, and that they grow more rapidly during pregnancy and lactation.

Carcinoma of the Breast

Carcinoma of the breast is one of the more important diseases of human beings. It con-

stitutes about 90 per cent of all tumors of the breast, 15 per cent of all malignant tumors in human beings and 30 per cent of all cancer in women (Pack and LeFevre).

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Pathologic Anatomy. Careful macroscopic examination of the breast is of the greatest importance, especially in the detection of small foci of malignant transformation in chronic cystic mastitis and other diseases. In primary mammary carcinoma there is typically a single, extremely firm, nonelastic nodule, which has

limited mobility. The nonelasticity and restriction of mobility serve in most instances to differentiate carcinoma from fibro-adenomas and cysts. When examined in cross section the nodule appears firm, grayish white, and fibrillar, with fine or coarse radiating trabeculae extending to the surrounding breast. In the main mass there are small yellow points and lines, less than 1 mm. in diameter, representing the epithelial elements and the necrotic debris within lumens. Carcinoma secondary to chronic cystic mastitis is to be recognized as a focal region of thickening and induration in the wall of a cyst, or as firm, fixed areas in the otherwise gray elastic translucent tissue (Muir).

Types of Carcinoma. Carcinoma simplex, alveolar carcinoma, adenomatoid carcinoma, and scirrhus carcinoma have the same gross

and microscopic appearance in the breast as in other parts of the body. The scirrhous carcinoma is a firm, irregular, illy defined nodule in the breast and is usually highly malignant. The common type is carcinoma simplex.

From a prognostic standpoint it is adequate to divide carcinoma of the lobules of the

trally about the nipple, and not over 5 to 10 per cent in each of the three other quadrants.

Local Metastases. In general the frequency of the metastases to the lymph nodes depends on age (they are more common in younger women), on the size of the primary lesion, and on the grade of the tumor. The two later points

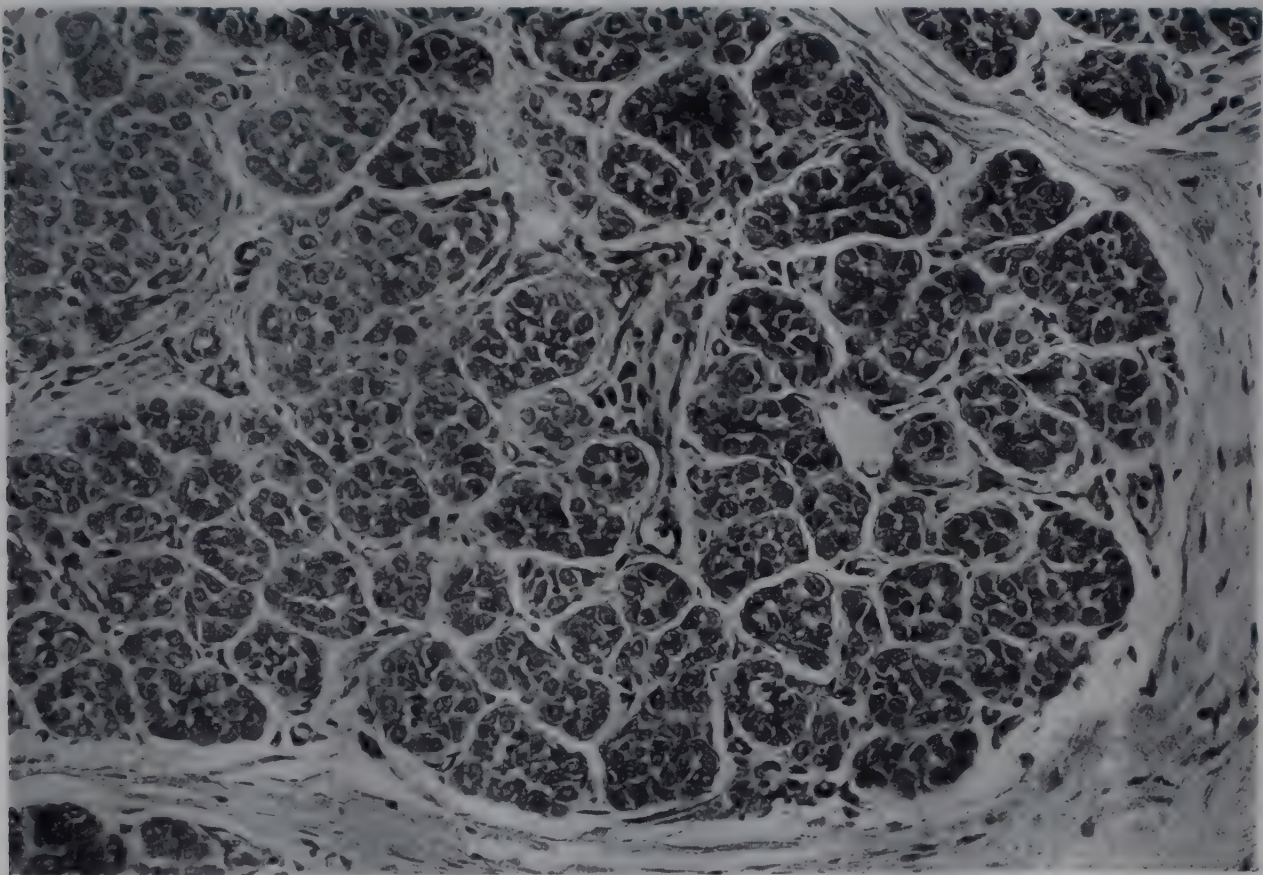


Fig. 447. Carcinoma in situ. (Photograph by courtesy of Dr. F. W. Foote, Jr.)

breast into infiltrating and noninfiltrating (carcinoma in situ) types (Foote and Stewart).

Carcinoma in Situ. In contrast with all other types of carcinoma of the breast, in this variety the usual signs of a malignant neoplasm are absent. On section only congeries of large compact lobules are seen. In the affected lobules the cells and nuclei are twice normal size and the cytoplasm is acidophilic and sometimes vacuolated. The lumens are filled with cells. Mitoses are rarely observed (Foote and Stewart).

Rare Types. Unusual forms of carcinoma of the breast of prognostic significance include the sweat gland or apocrine gland type of carcinoma, the carcinoma originating in the lining of a cyst, the spindle cell carcinoma (adenosarcoma), the adenoid cystic carcinoma, and the carcinoma with osseous and cartilaginous metaplasia (Foote and Stewart).

Location in the Breast. Approximately one-third of all carcinomas of the breast occur in the upper outer quadrant, about one-fifth cen-

are illustrated in the following tables (Taylor and Nathanson):

Size of the Primary Lesion	Percentage with Metastases to the Lymph Nodes
1 cm.....	25
4 cm.....	60
6 cm.....	94
9 cm. or more.....	100

Grade	
I.....	14
II.....	64
III.....	81

Distant Metastases. If carcinoma of the breast is the cause of death, there are usually widespread metastases throughout the viscera. In order of frequency the organs invaded are: pleura, lungs, liver, bones, brain, and kidneys. The metastases to the bones are osteoclastic, and the sternum, ribs, spine, and femur are most frequently affected (Sharpe and MacDonald).

Carcinoma of the Breast in Animals. All

types of tumors of the breast have been observed in both wild and domestic animals. Experimental studies of carcinoma of the breast in mice have yielded much valuable information concerning the nature and cause of carcinoma (see the discussion of causes of neoplasia in the chapter on tumors in general).

Incidence and Causal Factors. *Age.* Carcinomas of the breast are rare before the age of twenty. Twenty-six per cent occur before the age of forty, 42 per cent between the age of forty and five years after the menopause, and 32 per cent more than five years after the menopause.

Menstrual History and Ovarian Function. Most women with carcinoma of the breast have a normal menstrual history. However, at the time the tumor appears only 54 per cent of the patients have a regular four-week cycle, and this is true of both the younger and the older patients. Furthermore only 68 per cent have periods of normal length at the time of the appearance of the tumor—the trend is toward shorter periods.

Marital State and Fertility. While 11 per cent of American women are unmarried, 15 to 18 per cent of the patients with carcinoma of the breast are unmarried, according to most statistics. It has also been observed that 42 per cent of women with carcinoma of the breast are nulliparous, while only 33 per cent of women in the general population of the United States are nulliparous. The fertility in the general population and in women with carcinoma of the breast is essentially the same: 2.75 and 3.0 children per mother respectively.

Lactation. Of those patients with carcinoma of the breast who have had children, 40 to 50 per cent give a history of abnormal lactation, defined as having nursed none of their children, having nursed them less than three months, or having nursed only some of their children. If it is considered that the single state and the nulliparous state also represent a history of lactation abnormal for the average woman, then about 90 per cent give such a history. A small but significant number of women with carcinoma of the breast have inverted nipples, present from childhood. These observations are consistent with the experimental studies that show stagnation of milk in the breast as an important causal factor.

Heredity. Carcinoma of the breast in the

cancerous sisters of patients with carcinoma of the breast is far more common than carcinoma of other organs: one observer gives 45 per cent and 16 per cent respectively (Cramer). There is a suggestion of a “milk factor” (Wood and Darling).

Association with Other Carcinomas. If a patient with a carcinoma of the breast has another carcinoma, there are three chances out of five that this is a carcinoma of the cervix or uterus, suggesting a common causal factor and a close relation between malignant neoplasms of the secondary sexual organs, both stimulated by estrogenic hormones.

Trauma. If trauma were a factor in causing carcinoma of the breast it would be a far more common disease than it is.

Summary. All of these facts suggest a relation to the estrogenic hormones of the ovary, but it must remain for future investigation to establish the exact nature of the hormonal disturbance (MacDonald; Cramer; Adair and Bagg; and Taylor).

Prognosis. The most important points in the evaluation of prognosis are: stage of the disease at the time of the primary operation and the lapse of time between the appearance of the tumor and operation, as shown in the following table (MacDonald):

Percentage of All	
Stage of the Disease at Operation	Five-Year Survivals
Disease limited to the breast.....	53.8
Questionable invasion of the axillary nodes.....	11.6
Axillary nodes invaded.....	33.42
Supraclavicular nodes invaded.....	1.12
Remote metastases.....	0.06
Lapse of Time Between Recognition of Tumor and Operation	
Less than 3 months.....	44.6
More than 12 months.....	28.5

Paget's Disease

Pathologic Anatomy. In 1874 Sir James Paget wrote:

I believe it has not yet been published that certain chronic affections of the skin of the nipple and areola are very often succeeded by the formation of scirrhous cancer in the mammary gland. . . . The patients were all women, various in age from 40 to 60 or more years, having in common nothing remarkable but their disease. In all of them the disease began as an eruption on the nipple and areola. In the majority it had the appearance of a florid, intensely red, raw sur-



Fig. 448. Paget's disease of breast. (Photograph from the files of the Barnard Free Skin and Cancer Hospital.)

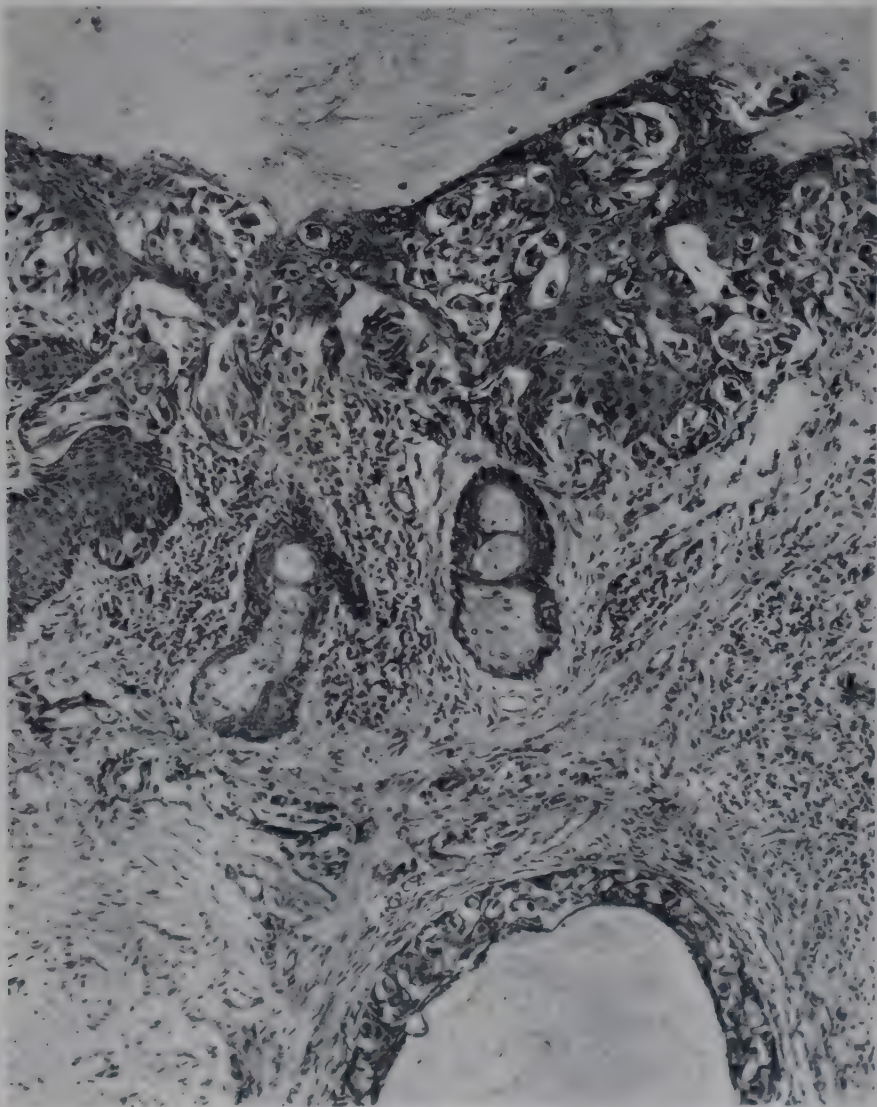


Fig. 449. Paget's disease. The epidermis is markedly acanthotic, and there is marked intracellular and extracellular edema. Large, vacuolated epithelial cells, which are devoid of intercellular bridges, the so-called "Paget cells," are present in the epidermis. The basal layer is disorganized. In the dermis there is an inflammatory infiltrate. In the lower right-hand corner of the photograph is a duct of the nipple. The cells lining this duct show changes similar to those found in the epidermis. (Photograph by courtesy of Dr. Zola Cooper.)

face, very finely granular as if nearly the whole thickness of the epidermis were removed; like the surface of very acute diffuse eczema or like that of an acute balanitis. From such a surface, on the whole or greater part of the nipple and areola there was always copious, clear, yellowish, viscid exudation. The sensations were commonly tingling, itching, and burning, but the malady was never attended by disturbance of the general health. . . . But it has happened that in every case which I have been able to watch cancer of the mammary gland has followed within at the most two years, and usually within one year.

The essential and characteristic feature of Paget's disease is the presence of peculiar cells in the epidermis of the nipple, spoken of as "Paget's cells." They are more numerous and largest in the rete. The individual cells are large, round or oval, and have an abundant, lightly acidophilic cytoplasm, and large vesicular or hyperchromatic nuclei with large nucleoli. Mitoses are present. The surrounding epithelium is compressed. The dermis is not invaded, but within it there are edema, hyperemia, and infiltration with plasma cells and lymphocytes.

Pathogenesis. Careful histologic studies support the concept that the Paget cell is a neoplastic cell and hence that the areolar lesion is an intraepidermal invasion by a pre-existing intraductal carcinoma of a low grade of malignancy (Muir). It is possible that a lesion of similar appearance may rarely be caused by other basic diseases.

Extramammary Paget's Disease. Epidermal changes identical with those of Paget's disease are rarely seen in other regions of the body, usually over an underlying carcinoma of sweat glands (Parsons and Lohlein).

Sarcoma of the Breast

Sarcoma of the breast comprises less than 1 per cent of all tumors of the breast. The usual type is the "adenofibrosarcoma," also called "cystosarcoma phyllodes," probably derived from a preexisting fibro-adenoma. In the primary sarcomas of the breast the spindle cell and the round cell types are the most common. Liposarcoma has been reported. Metastases to the lymph nodes of the axilla are found in less than 5 per cent (Hill and Stout).

Sarcoma of the breast may occur at any age from childhood on, and a definite history of trauma is secured in about 10 per cent. The tumors tend to recur, but the prognosis in general is good.

Carcinoma of the Male Breast

Carcinoma of the male breast is similar in all gross and microscopic features to carcinoma of the female breast. Adenocarcinoma is the most common histologic type. Squamous cell carcinoma and Paget's disease each constitute less than 1 per cent of all tumors of the male breast. Metastases are most common in the lungs, pleura, ribs, spine, and liver.

Incidence. Carcinoma of the male breast represents about 0.7 per cent of carcinoma in the male and is about one-hundredth as common as carcinoma of the female breast. The highest incidence is between the ages of fifty-five and sixty-five. The two breasts are involved with equal frequency and bilateral carcinoma has been recorded.

Causal Factors. No definite causal factors are known. A history of trauma is secured in about 25 per cent of patients, and in about 15 per cent there is a preceding gynecomastia (Gilbert).

Clinicopathologic Correlation. Pain, retraction of the nipple, bleeding from the nipple, and ulceration are the principal signs and symptoms, as in carcinoma of the female breast. Five-year survivals free of the disease do not exceed 20 per cent. A few carcinomas of the male breast apparently originate in benign tumors which have been present for many years (Sachs). Orchiectomy has given some improvement (Farrow and Adair).

Miscellaneous Lesions of the Male Breast. Acute mastitis in the male breast has the usual characteristics of an inflammation. Chronic mastitides of the types found in the female breast are rare, but when present are typical. Benign tumors constitute about two-thirds of all tumors of the male breast, and the most common is the fibro-adenoma (Neal and Simpson). Sarcoma of the male breast is rare.

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CIV

Diseases of the Male Secondary Sexual Organs

The prostate, seminal vesicles, vasa deferentia, and penis are the male secondary sexual organs to be discussed here, although many other tissues and organs depend in whole or in part on the internal secretory activity of the testes, and might, therefore, be regarded as secondary sexual organs.

fortieth to the sixtieth years of life. During this time the outstanding characteristic is the variation in the appearance of the same structure in different parts. In the stroma there are atrophy of the smooth muscle fibers and a relative increase in connective tissue. The collagen becomes denser and more homogeneous.

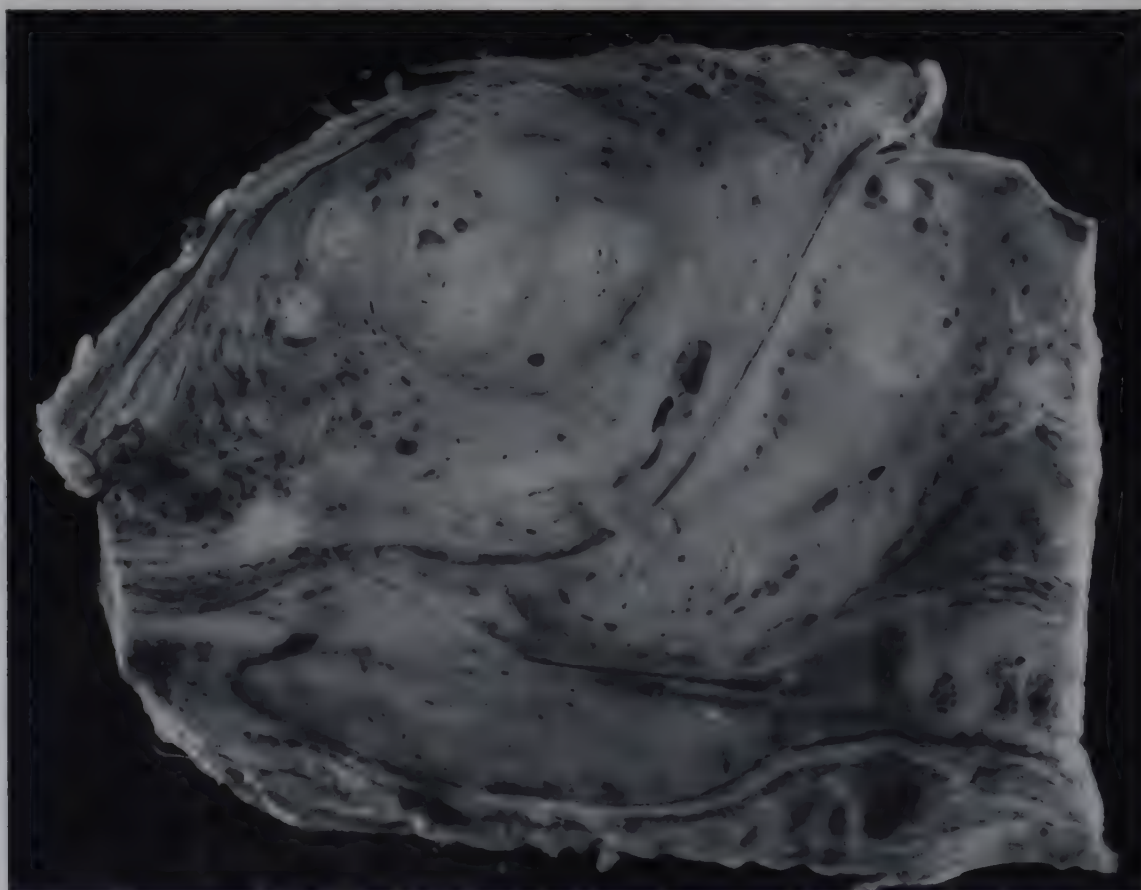


Fig. 450. Nodular hyperplasia of prostate. (From material reported by Moore: J. Urol., Vol. 50.)

Morphologic Changes in the Prostate with Increasing Age. The normal prostate gland increases slightly but progressively in size from the third to the ninth decade of life. At the end of the fourth decade and at the beginning of the fifth, unmistakable histologic changes occur, which are, so far as can be determined, independent of any recognized disease process. These changes occur progressively, but they are conveniently grouped into those of the presenile period and those of the senile period. The presenile period extends from the

The acini remain large, but the papillae are less numerous, and the epithelial cells tend more to the cuboidal type. This atrophy occurs irregularly throughout the gland, being advanced in one lobule and inconspicuous or absent in another lobule.

In the prostate of a person over sixty, the processes are more static and progress more slowly. The greater part of the organ is involved, and there is less variation from lobule to lobule. In focal areas the acini undergo complete atrophy, and are replaced by a mass

of loose connective tissue. Within the acini, numerous corpora amylacea are formed, probably as the result of stagnation of secretion and loss of the muscular activity of the organ. It is possible to estimate the age of a man by gross and microscopic examination of the prostate (Moore).

Prostatic Calculi

Most concretions in the prostate—corpora amylacea and small calculi—are incidental

findings, and produce neither signs nor symptoms (Moore; Moore and Hanzel). Occasionally larger calculi may form, and, especially if associated with infection, cause symptoms of urinary obstruction. The stones are usually faceted, and vary in composition: calcium and magnesium phosphate and calcium oxalate. It is possible that some are urinary stones which have become embedded in the prostate. The diagnosis is best established by radiographic examination.

and inelastic, although on occasion some nodularity may be apparent. The tissue is divided into two parts: a peripheral segment measuring from 2 to 5 m. in thickness, completely surrounding a central, bulging, nodular part on the lateral and posterior aspects. The peripheral portion is grayish white and firm, and represents compression of the preexisting normal prostate before the development of nodular hyperplasia. The central portion may be divided into three parts, a large mass on each side of the prostatic urethra, and a mass projecting into the bladder at the vesicle neck. This latter portion has no connection with the anatomic middle lobe of the prostate. Each of these masses is composed of numerous small spherical nodules, some of which are grayish white and fibrillar. Most of the nodules contain glandular structures appearing as small yellow or gray dots or as dilated cavities.

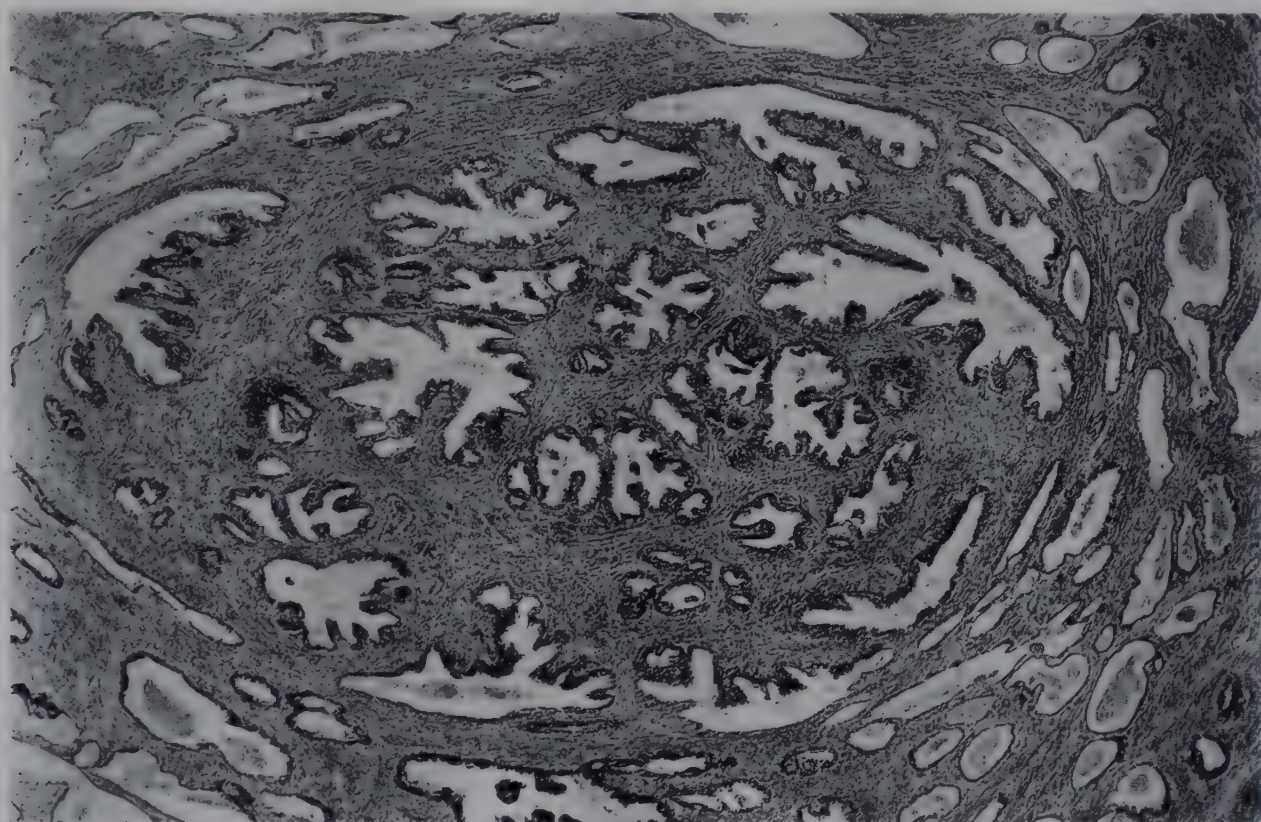


Fig. 451. Nodular hyperplasia of prostate. (Cowdry: Problems of Ageing, Williams and Wilkins.)

Nodular Hyperplasia of the Prostate

For this disease tradition and common usage dictate the term "benign hypertrophy." The disease is not a form of hypertrophy but of hyperplasia, and by definition both hyperplasias and hypertrophies are benign and need not be so designated. A more desirable designation, therefore, is "nodular hyperplasia" of the prostate. The term "prostatism" is a clinical designation for all conditions which produce obstruction to the flow of urine from the bladder into the penile urethra. It should not be used synonymously with "nodular hyperplasia," for there are numerous other conditions leading to prostatism.

Pathologic Anatomy. In the advanced or clinically manifest disease, the prostate is enlarged to two or three times normal size. The capsule is tense and the tissue uniformly firm

For this disease tradition and common usage dictate the term "benign hypertrophy." The disease is not a form of hypertrophy but of hyperplasia, and by definition both hyperplasias and hypertrophies are benign and need not be so designated. A more desirable designation, therefore, is "nodular hyperplasia" of the prostate. The term "prostatism" is a clinical designation for all conditions which produce obstruction to the flow of urine from the bladder into the penile urethra. It should not be used synonymously with "nodular hyperplasia," for there are numerous other conditions leading to prostatism.

The nodules are composed of stroma and epithelial acini. The stroma is composed of both connective tissue and smooth muscle, and the cells are more closely packed, with less intracellular substance, than the normal stroma. There are no mitotic figures. The epithelium is arranged in definite acinic structure with two layers of cells. The luminal layer is tall columnar with a basal nucleus and some slight activity of apocrine secretion in the peripheral part of the cytoplasm. The basal layer of cells is not continuous, and is made up of cuboidal flattened cells, each with a round chromatic nucleus. At the edge of most nodules there is a characteristic and pathognomonic area of the acini known as "encircling glands." A single gland may stretch for from one-third to one-eighth of the circumference of a nodule. The epithelium on the side of this gland adjacent to the nodule is tall columnar, and numerous invaginations extend into the stroma of the nodule. The cells on the outside of the gland are low cuboidal and flattened and show no evidence of hyperplasia.

Secondary Changes. In from one-fourth to one-half of all instances of nodular hyperplasia there are evidences of healed or recent infarcts. About the healing infarcts and in the healed infarcts there are solid masses of squamous epithelium (apparently the reaction of the prostatic epithelium to necrosis), which are frequently and incorrectly interpreted as carcinoma. The ductal system in nodular hyperplasia empties into the urethra. Occasionally, these ducts become occluded, and inspissated secretion accumulates in the acini. This is positively chemotactic for leukocytes that accumulate within the lumen and in the surrounding stroma. The epithelial cells undergo necrosis and atrophy.

Histogenesis. The smallest and presumably the earliest lesion of nodular hyperplasia may be one of three types: a stromal nodule in the wall of the urethra, concentric and eccentric growth of stroma about one of the larger prostatic ducts, or focal proliferation of both stroma and glands in the lateral lobe of the prostate. Nodules are rarely, if ever, formed in the posterior and anterior lobes.

Incidence and Causal Factors. Nodular hyperplasia is a common disease of elderly men. During the past hundred years many theories have been proposed to explain nodular hyperplasia. The more important of these theories

are chronic inflammation, arteriosclerosis, and hormonal dysfunction. The last seems the most probable with our present knowledge, and is strongly supported by many observations. Nodular hyperplasia rarely occurs before the age of forty, and is, therefore, distinctly a disease of the senescent part of life, when it is known that there is a decrease in the urinary excretion of both androgens and estrogens. It has never been reported in a eunuch, suggesting that the testis is a necessary causal factor. It occurs in a gland undergoing atrophy. The most likely theory is that during presenility and senility there is a decrease in the total hormonal stimulation, and a disturbance in the ratio of the androgens to the estrogens.

Relation to Carcinoma. It has been repeatedly shown that less than 2 per cent of cases of nodular hyperplasia are associated with true carcinoma. Confusion has arisen largely because of the failure to recognize that carcinoma may originate in the posterior lobe and secondarily invade the region of nodular hyperplasia. Nodular hyperplasia and carcinoma of the prostate occur together and independently with equal frequency, indicating that they are not related diseases beyond the fact that they occur in the same age groups.

Clinicopathologic Correlation. The outstanding symptoms of nodular hyperplasia are urinary frequency, difficulty in starting the stream, and dysuria. These are directly related to obstruction of the prostatic urethra, but there is no correlation between the size of the prostate and the degree of obstruction. It is possible that the obstruction is physiologic, from a disturbance of the muscles of the internal sphincter. The bulge of the nodule into the bladder along the posterior lip of the internal sphincter makes complete emptying of the bladder impossible, and thus after each micturition from 100 to 500 cc. of urine is retained. This residual urine becomes infected. The obstruction leads to hypertrophy and dilatation of the bladder. The retention of urine and the infection in about one-fourth of the cases result in the formation of vesical calculi. The ureters and renal pelves are the seat of an acute and subacute inflammation. Within the kidney there is a diffuse interstitial inflammation and the formation of multiple abscesses. The changes in the renal pelvis and in the kidney are responsible for the uremia which fre-

quently develops terminally in these patients. In a few persons the infection extends through the genital tract, and there is a unilateral or bilateral epididymitis (Moore).

Carcinoma of the Prostate

Types. A proper evaluation of carcinoma of the prostate involves not only a study of the clinically manifest cases, but also the recognition that about 20 per cent of all men beyond the age of fifty have a histologically demonstrable carcinoma of the prostate. This latter

normal prostate. Rarer types are the small cell carcinoma, the lipoid-rich carcinoma, and carcinoma simplex.

Invasion and Metastases. When a carcinoma of the prostate reaches 2 or 3 mm. in diameter, there is invasion of the lymphatic spaces and extension to the capsule. Within the lymphatic vessels the tumor extends to the wall and capsule of the seminal vesicles. When the greater part of the organ has become involved, tumor tissue is found in the floor of the bladder adjacent to the internal sphincter. True metastases occur first to the lymph nodes

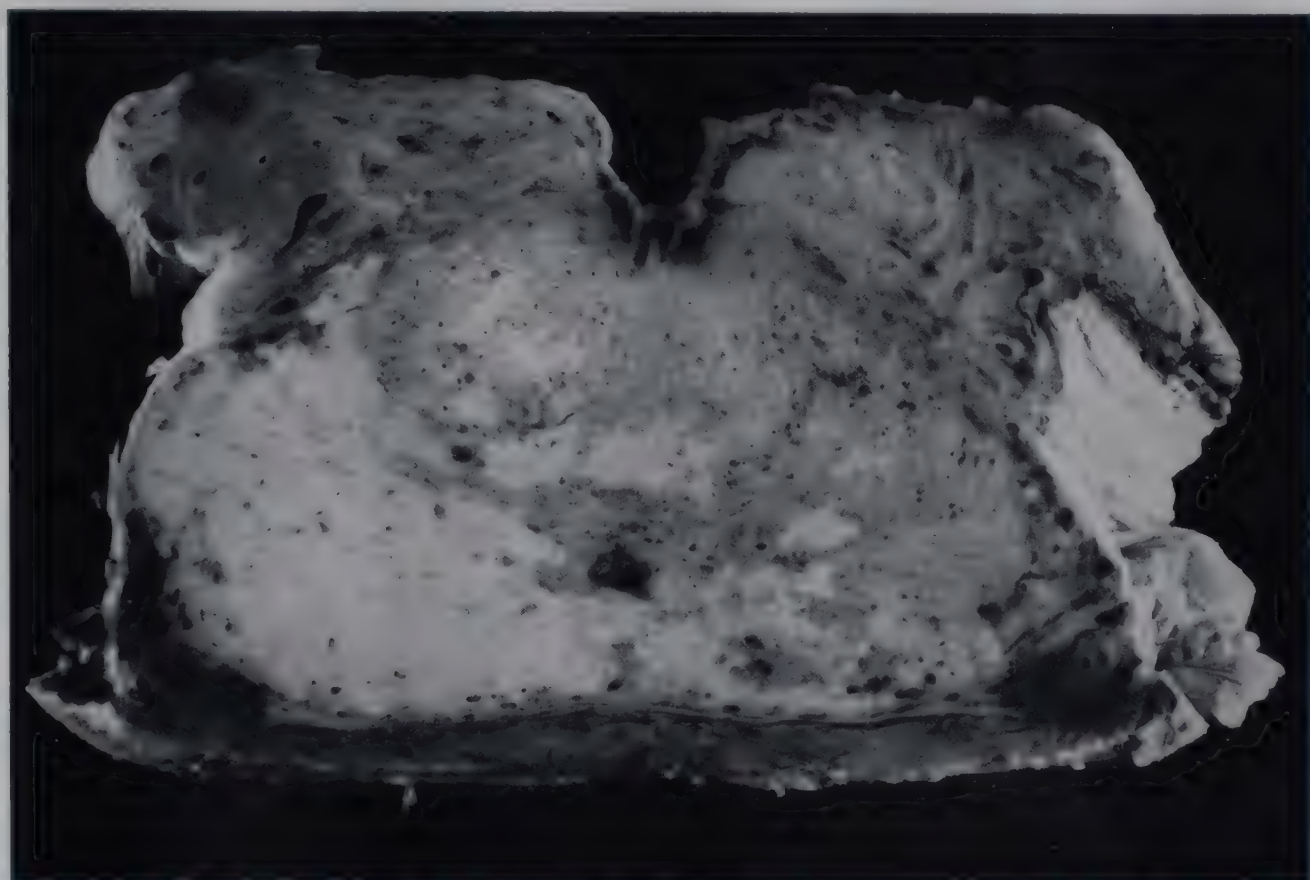


Fig. 452. Carcinoma of prostate. (From material reported by Moore: J. Urol., Vol. 33.)

type of lesion is conveniently designated as "latent carcinoma." "Occult carcinoma" designates a type of case in which there are widespread metastases producing clinical signs and symptoms, but in which the tumor of the prostate is small and frequently not recognized.

Pathologic Anatomy. About 75 per cent of all cases of carcinoma of the prostate originate in the posterior lobe and appear as grayish white, firm, infiltrating masses (Moore).

The commonest type is the adenocarcinoma. The cells are arranged in definite and regular acinic structure. The individual cells are cuboidal or low columnar and show no evidence of secretory activity. About the acini, the stroma is arranged irregularly with no semblance of the thin layer of collagen and the slings of muscle so characteristic of the

about the internal iliac artery and then to the periaortic lymph nodes. From these latter lymph nodes, tumor cells extend directly into the vertebral bodies. Distant metastases are commonest in the lungs and liver.

Histogenesis. With a few exceptions carcinoma arises in a prostate which is the seat of preexisting atrophy. Histologic studies show that one or more foci of atrophic epithelial cells undergo malignant transformation and invade the surrounding stroma.

Incidence. In a series of autopsy studies on unselected carcinomas, eleven were found to be clinically manifest and fifty-two latent. That the latent carcinomas develop into clinically manifest tumors if the patient lives long enough is indicated by the fact that carcinoma of the prostate increases with increasing age,

so that after seventy-five it constitutes 30 per cent of all malignant tumors.

Clinicopathologic Correlation. About the only symptom which carcinoma of the prostate can produce is obstruction of the prostatic urethra. Unfortunately, carcinoma of the prostate is most frequently in that part of the gland far removed from the urethra, and hence gives no symptoms until it has progressed to the

neoplastic cells (Schenken, Burns, and Kahle).

Sarcoma of the Prostate. Sarcoma of the prostate is rare. About one-half of cases are in children. The tumors are bulky, and grow into and fill the bladder. Histologic types are rhabdomyosarcoma, leiomyosarcoma, fibrosarcoma, and lymphosarcoma (Melicow, Pelton, and Fish).

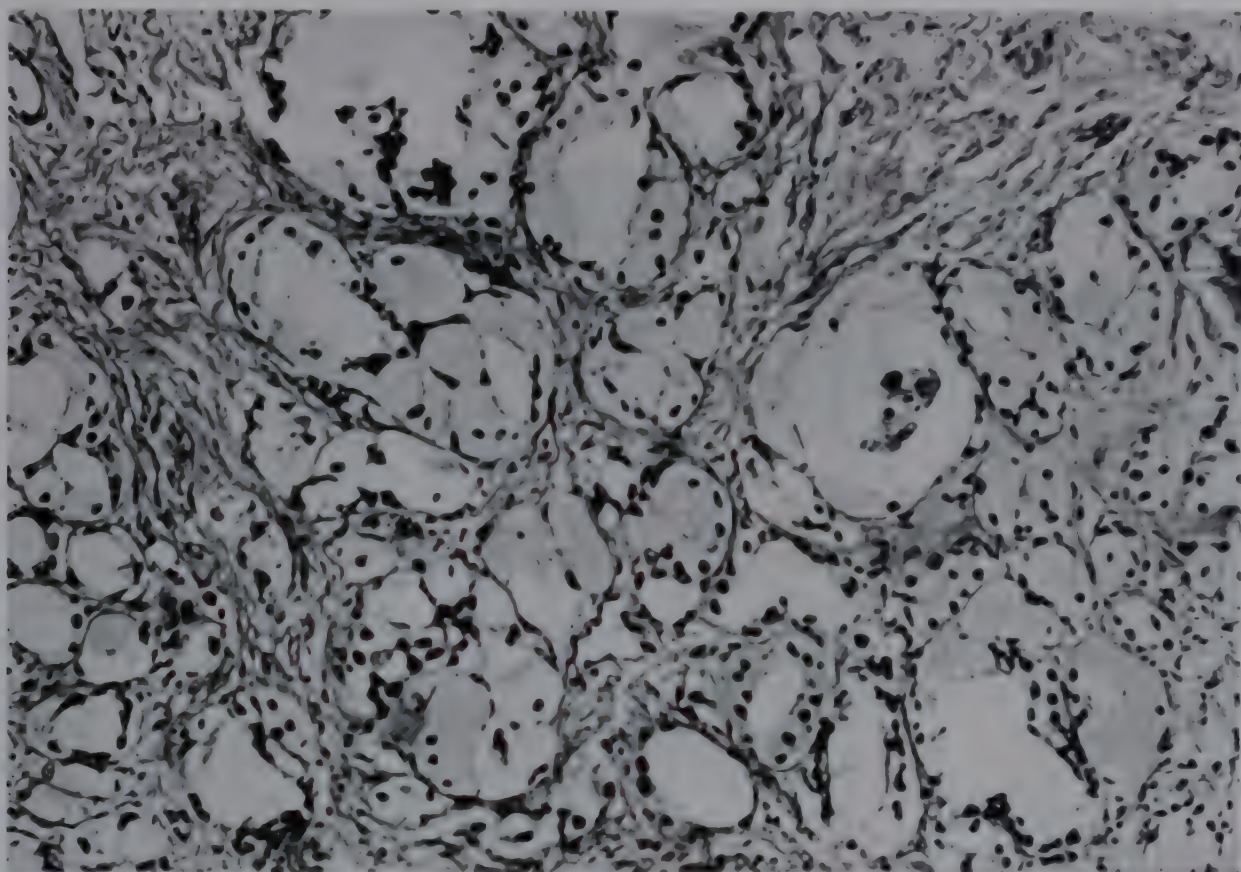


Fig. 453. Carcinoma of prostate after treatment with stilbestrol. (Slide by courtesy of Dr. Carl Waltenberg and Dr. D. K. Rose.)

point of invasion of the surrounding tissues and is no longer amenable to surgical removal. The focus of carcinoma is a hard, circumscribed nodule. When the vesicles are invaded, they are enlarged and firm. Carcinoma of the prostate grows slowly and, except for occult carcinoma, does not give rise to metastases before it invades the urethra and produces urinary obstruction. Histologic grades of carcinoma of the prostate are correlated with prognosis and for the three grades the average duration of life is six, twelve, and eighteen months, respectively.

Physiologic Aspects. In most patients there is an increase of the serum acid phosphatase and, if bony metastases are present, of the serum alkaline phosphatase also (Huggins, Scott, and Hodges).

Effect of Estrogens and Castration. Treatment with stilbestrol or by castration brings about fatty degeneration and atrophy of the

Epidermoid Carcinoma of the Penis

Carcinoma of the penis constitutes about 2 per cent of all malignant tumors in men (Naegele).

Pathologic Anatomy. The site of predilection is the glans and prepuce. The initial lesion is a papilloma or a subepithelial nodule under a phimotic prepuce. Subsequent growth is either as a fungating papillary tumor or an infiltrating type of neoplasm. Invasion through the fascial planes into the corpora is rare. Secondary infection is common, and a bloody, offensive discharge is present. The microscopic structure is that of an epidermoid carcinoma.

Metastasis to the inguinal nodes is present in about half of the patients when they first seek advice. Visceral metastases occur late, most frequently to the liver.

Causal Factors and Incidence. Carcinoma of the penis is a disease of noncircumcised men

from forty to seventy years of age, hence it is extremely rare in Jewish persons and in Mohammedans, and most frequent in Chinese and Hindus. Preceding lesions such as the scar of a circumcision or chancre, trauma, and acuminate condylomas have been reported.

Clinicopathologic Correlation. There are no early symptoms except discharge because of the location of the carcinoma beneath the prepuce. By the time the ulcerated tumor is visible, regional metastases are present. Most tumors are radioresistant. Radical resection gives only about 20 per cent five-year survivals.

Other Tumors of the Penis. The only other important neoplasm of the penis is the vascular tumor variously termed "angioma" or "endothelioma" of the corpora cavernosa. There are numerous vascular channels and large pale cells, apparently arising from endothelium. Distant metastases may be observed (Rabson; Foulds and Flett).

Carcinoma of the Scrotum. Epidermoid carcinoma of the skin of the scrotum is an occupational cancer of chimney-sweeps and mule-spinners. The initial lesion, a papule, ulcerates, and metastases develop in the inguinal nodes. Most are of a low grade of malignancy.

Miscellaneous Diseases of the Male Secondary Sexual Organs

Phimosis. Phimosis is the condition in which the prepuce cannot be drawn back over the glans. A certain degree is normal at birth, but later may be responsible for inflammation and formation of adhesions. Calculi are occasionally deposited in the smegma beneath the prepuce. Extreme types of phimosis lead to urinary obstruction and infection.

Inability to reduce the prepuce from its retracted position above the glans is paraphimosis. There is obstruction of the vascular return and consequent extreme edema of the glans.

Priapism. Priapism is a prolonged and persistent erection of sudden onset unaccompanied by sexual desire. The cause may be nervous or local mechanical.

Peyronie's Disease. This is a plastic induration of the corpora cavernosa of the penis, composed of dense, white, fibrous tissue in the form of plaques. Eventually part or all of the collagen may calcify. The cause is unknown, and treatment is unsatisfactory (Wesson).

Diseases of the Seminal Vesicle. Aside from acute and chronic gonococcal seminal vesiculitis and the changes of increasing age, atrophy and fibrosis, lesions of the vesicles are rare: calculi, cysts, and carcinoma. It is remarkable that two organs both under control of the androgens, the prostate and the vesicles, are so dissimilar. Carcinoma of the prostate is a common disease. Carcinoma of the seminal vesicles is one of the rarest forms of cancer, if it has ever been observed.

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CV

Increased Intracranial Pressure and Hydrocephalus

The brain and spinal cord are contained within a bony case. After closure of the sutures in childhood no increase in size is possible, and the presence of a space-consuming lesion inevitably results in all the changes of increased intracranial pressure.

Anatomic Considerations. A clear concept of this problem rests on an understanding of the anatomic structures. The relatively solid brain is actually a hollow viscus, suspended in a fluid. The fluid in the ventricles is in free communication with the fluid in the subarachnoidal space. The brain itself is the wall of the hollow viscus. The fluid is formed in the choroid plexus inside, and is resorbed by the pacchionian granulations on the outside. Any obstruction of the flow of fluid from the source in the lateral ventricles through the foramens of Monro, the third ventricle, the aqueduct of Sylvius, the fourth ventricle, the foramens of Magendie and the foramen of Luschka, and the subarachnoidal space to the granulations on the convexity of the hemispheres, will cause dilatation of the system proximal to the obstruction, and a demand for more intracranial space. In an exactly analogous manner a tumor growing in the brain or in the meninges or a hemorrhage into the intracranial tissues will occupy space that was formerly tissue or fluid.

The Primary Effects of Increased Intracranial Pressure

The initial reaction to a space-consuming lesion in the cranial cavity is reduction in the amount of fluid, and herniation through the foramens in the skull.

Changes in the Size and Position of the Ventricles. With a focal lesion such as a tumor or hemorrhage in proximity to the ventricular system, the available space may be increased by collapse of the ventricle. As more space is needed, the involved ventricle may be

pushed to the opposite side or upward or downward, depending on the position of the lesion (Fig. 456, p. 932). The shift in position or change in size may involve an entire ventricle or only part of it. Similarly a focal lesion may obstruct one foramen of Monro or the aqueduct, and produce dilatation of one or both lateral ventricles. These changes in size and position are readily demonstrable by ventriculography.

Changes in the Convolution and Sulci. Normally each convolution of the brain is rounded and the intervening space between adjacent convolutions is filled with cerebrospinal fluid. As all or a part of the brain increases in size, the fluid between the convolutions is pushed out; and as seen at autopsy the convolutions are flattened and the sulci are narrow and shallow. The obliteration of subarachnoidal space leads to disturbance in the flow of fluid from the base to the convexity, and to a certain degree of communicating hydrocephalus.

Changes in the Circulation. The venous pressure in the dural sinuses is low, and the venous channels may be compressed when there is increased intracranial pressure. Under these conditions the normal venous return is impeded and chronic passive hyperemia ensues. Examination of the ocular fundi may show engorgement of the retinal branches of the ophthalmic vein that drains into the cavernous sinus. As the pressure of the brain rises above that in the sinus, small hernias of nervous tissue form through the weak points in the walls of the sinus (Wolbach).

Changes at the Foramens. Each of the nerves, arteries, and veins enters or leaves through a perforation in the bony skull. These foramens are weak points, and increasing pressure will be expended through them.

Pressure of the Optic Foramen. The optic



Fig. 454. Erosion of internal table of skull in a patient with increased intracranial pressure incident to a tumor of the third ventricle. (Radiograph by courtesy of Dr. Sherwood Moore, M.I.R., 156901.)



Fig. 455. Cerebellar pressure cone.

nerve is covered by dura mater, and increased pressure transmitted through the nerve, together with the partially blocked venous return, causes bulging of the nerve head into the vitreous. This lesion, known as "papilledema" or "choked disk," is readily seen with an ophthalmoscope.

Distribution of Pressure. In a discussion of the effects of pressure, the cranial cavity must be divided into three communicating cavities: a right, a left, and a posterior. The firm, fibrous, dividing membranes are the falx cerebri and the tentorium cerebelli. Increases in pressure with focal lesions are greater in the



Fig. 456. Displacement and compression of the left lateral ventricle by a brain tumor. (Radiograph by courtesy of Dr. Sherwood Moore, M.I.R. 143381.)

Pressure at the Foramen Magnum. As the pressure within the skull increases, the medulla and cerebellum, occupying the most caudal part of the cranial cavity, are forced downward into the spinal canal through the foramen magnum. In time the cerebellar tonsils are molded to produce a deformity known as a "cerebellar pressure cone" (Fig. 455). In order to support the increased intracranial pressure the pressure of the fluid in the subarachnoid space about the cord is elevated so that the brain is held on a column of spinal fluid. Sudden release of the spinal pressure by lumbar puncture may allow impaction of the medulla into the foramen, with respiratory failure.

cavity affected than in the other two. After a time, however, the pressure is dissipated to all parts, and the secondary changes are equal.

Secondary Effects of Increased Intracranial Pressure

All of the effects so far discussed are *reversible*. Obliteration of space occupied by fluid, and utilization of the proximal parts of the foramens, may make available an estimated volume of 50 to 100 cc. But as the tumor, hemorrhage, or hydrocephalus grows in size, certain *irreversible* alterations in the intracranial tissues and the skull must take place. These are designated as "secondary effects."

Changes in the Brain. Constantly increasing pressure on the brain by an expanding tumor or by an internal hydrocephalus causes atrophy of nervous tissue. Internal hydrocephalus in young children caused by congenital or acquired atresia of the aqueduct of Sylvius is an illustration. The skull gives at the sutures, but not enough to make up for the increasing size of the ventricles. The medulla, not involved in the internal hydrocephalus and partially protected from the pressure by the tentorium, continues to function, and hence life is possible. The cerebral hemispheres are caught between the outward pressure of the ventricles and the inward pressure of the skull, and in extreme cases may not measure over 1 mm. in thickness. There is in most instances conspicuous mental retardation, and sometimes idiocy. In the adult, whose bony cranium is unyielding, there is less dilatation of the ventricles and atrophy of the brain, and death from internal pressure occurs early. Herniation of the brain through weak points in the dura and erosion of the overlying skull may be observed (Wolbach). In the compressed nervous tissue in both examples there are loss of ganglion cells and proliferation of astrocytes.

Changes in the Skull. Although the skull of the adult will not expand, long-continued pressure against the internal table by each of the convolutions induces atrophy or resorption of bone, greater over the convolutions than over the sulci—digitation of the skull (Fig. 454, p. 931). In children, as the internal table is resorbed, new bone is deposited in perpendicular trabeculae on the outside of the external table, so that in the end a head twice normal size may have a calvarium approaching normal thickness.

Changes in the Cranial Nerves and at the Foramina. Continued pressure over long periods of time induces degenerative changes in the nerves. Thus, early blindness is caused by edema and swelling of the optic nerve, but later permanent blindness results from degeneration of the axis cylinders. In other focal

lesions a nerve or a tract may be stretched to the point at which function is lost. In general increases of pressure, the brain may be forced into the foramina and may secondarily press on the nerves to produce degeneration.

Causes and Types of Hydrocephalus

An increased quantity of cerebrospinal fluid, either generally or locally, may logically be accounted for by one of three mechanisms: (1) an increased rate of secretion, (2) a decreased rate of resorption, and (3) a block in the flow of fluid between the ventricles and the pacchionian granulations. The third type, or obstructive hydrocephalus, is the form usually encountered. Two general varieties are recognized: internal hydrocephalus, if the obstruction is rostral to the fourth ventricle, and communicating hydrocephalus, if the obstruction is in the subarachnoid space (Dandy and Blackfan).

Internal hydrocephalus may result from congenital atresia or stenosis of the aqueduct of Sylvius, from tumors or cysts pressing on and occluding the narrower parts of the ventricular system, and from fibrous obliteration of the foramina of the fourth ventricle by an inflammatory process.

Communicating hydrocephalus is almost always caused by fibrous obliteration of the subarachnoid space over the lateral aspects of the base of the brain and over the convexities of the cerebral hemispheres incident to organization of the exudate in a prenatal or postnatal leptomeningitis. A peculiar type of communicating hydrocephalus is discussed in the section on spina bifida.

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CVI

Diseases of the Neuromuscular System Related to Hereditary Factors— Lethal Genes

In one group of diseases of the nervous and muscular systems, differing from most others, the human being appears anatomically and physiologically normal during intra-uterine life and during early development. In from a few months to seventy years after birth a specific type of cell undergoes degeneration, with no apparent exciting cause. There is evidence, however, of a familial or hereditary influence; 90 per cent of the members of a family may show some variation of the total disease.

The most logical explanation of this category of disease is the theory of the *lethal gene*. For example, it may be assumed that the life expectancy of the human being, barring premature death from disease or accident, is about one hundred years. At that age certain cells essential to life retrogress and are no longer able to function. In certain families one or more genes may determine that some cells shall retrogress before the allotted life span of the race as a whole. Similarly one or more genes may delineate the localization of the degeneration. These are known as "lethal genes."

This theory is strongly supported by the experiments of Stockard. He and many dog fanciers had noted that some St. Bernards and Great Danes acquire a distinctive type of paralysis of the hind legs during middle or late puppyhood. By selective cross-breeding he was able to secure F_1 hybrids that almost always did so. In the spinal cords of affected dogs there was a rapidly progressing degeneration of the motor and sympathetic neurons of a sharply limited segment, starting at about three months of age. Further study revealed that three dominant genes determine the degeneration, the time of onset, and the localization (Stockard).

More intensive investigations in what Stockard calls "experimental morphology," particularly in correlation with endocrine factors, may quite possibly give clues to the causes of many diseases.

Diseases of the Muscles

Familial Periodic Paralysis (Cavaré). This peculiar type of paralysis appears at about puberty with equal frequency in both sexes. There are irregular attacks of periodic flaccid paralysis of the arms and legs, lasting from a few hours to a few days, with completely asymptomatic intervals. Attacks can be precipitated by cooling of the muscles. Histologic examination of the muscles shows them to be essentially normal. Some patients have an associated hyperthyroidism and a disturbance in the metabolism of potassium (Ziegler).

Progressive Muscular Dystrophy (Erb-Landouzy). Progressive muscular dystrophy probably represents a complex familial disorder involving both the muscles and the endocrine glands. The muscles are atrophic and are replaced by fat. There is an increase of connective tissue between the atrophic fibers and an increase of adipose tissue. There is an increase in the sarcolemmal cells, and at times an apparent increase in the number of nuclei within the muscle cells. The blood vessels are thickened. There are no changes in the central nervous system. Varied alterations in the endocrine glands have been reported. The disease begins during childhood, is more common in boys than girls, and is frequently associated with other congenital anomalies.

Congenital Myotonia. Congenital myotonia is hereditary and is transmitted as a single dominant factor. It usually begins during the first and second decades of life, and increases

in severity, with periods of exacerbation and remission. The muscles are greatly enlarged, giving the patient an athletic appearance. The individual fibers show an enormous hypertrophy, and the number of sarcolemmal cells is increased. The transverse striations in the muscle are indistinct, and there may be vacuolation of the fibers. A slight increase of interstitial tissue is occasionally present. Clinical correlation is difficult to explain, in view of the fact that these hypertrophic muscles are incapable, especially under excitement or fright, of coordinated voluntary effort.

Myotonic Dystrophy (Déléage). In this condition there is eventual complete atrophy of the muscle fibers, leaving columns of sarcolemmal cells. There is slight proliferation of connective tissue, but no cellular infiltration. It is more common in men than women in a ratio of 5 to 1, and has its onset between the ages of twenty and thirty-five. It is definitely hereditary and involves principally the muscles of the face and neck, producing the so-called "hatchet face." Cataract, frontal baldness, atrophy of the testes, and osteoporosis of the bones are often associated.

Diseases of the Nervous System

Infantile Muscular Atrophy (Werdnig-Hoffman). The pathologic changes in infantile muscular atrophy are essentially the same as those in progressive muscular atrophy and in amyotrophic lateral sclerosis (p. 944). The primary lesion is in the spinal cord, and the atrophy of the muscle is secondary. It is familial and the first symptoms appear within a few weeks or months after birth. Few patients survive into adulthood. The muscles of the trunk and of the legs are most frequently affected.

Hypertrophic Neuritis (Déjérine-Soltz). The peripheral nerves are greatly increased in size and are irregularly tortuous. There is proliferation of the cells of the sheath of Schwann, with demyelination of the axis cylinders. There is a similar demyelination in the dorsal columns of the spinal cord and rarely in the pyramidal tract and in the optic nerves. The condition is familial and begins during the first or second decade of life. The muscles supplied by the involved nerves show the usual picture of neurotropic atrophy.

Peroneal Muscular Atrophy (Charcot-Marie-Tooth). The primary lesion is appar-

ently degeneration of the ventral horn cells of the spinal cord, the fibers of which innervate the peroneal muscles. There is corresponding degeneration of the ventral roots and of the peripheral nerves. In the more advanced cases there is degeneration of the cells in the dorsal horns and columns in the same levels of the cord. It is transmitted as a dominant and sometimes sex-linked characteristic. It appears in the first decade, and the atrophy of the peroneal muscles follows the usual course of a neurotropic atrophy.

Huntington's Chorea. The salient pathologic changes in Huntington's chorea are chromatolysis, fatty degeneration, and dendritic atrophy of the ganglion cells of the third, fifth, and sixth layers of the cerebral cortex and of the basal ganglia, notably the putamen and caudate nucleus. There is moderate hyperplasia of astrocytes. This results in convolitional atrophy and internal hydrocephalus of moderate grade. The leptomeninges are thickened, grayish white, and opaque, as a result of proliferation of the meningeal cells and cellular infiltration with lymphocytes. Subdural hematomas are occasionally seen. The blood vessels are thickened. There are demyelination and loss of the radiate tracts originating in the involved areas. Rarely there are similar lesions of the dentate nucleus.

Correlation of the anatomic changes with the mental retardation and the chorea, the onset in adult life, and the progressive course is difficult. The familial hereditary factor in most families is dominant. The average age of onset is thirty-five to forty years. Death from intercurrent disease or exhaustion follows in fifteen to twenty years. There is no treatment.

Tuberous Sclerosis. This is a special variety of cerebral sclerosis having its onset in childhood, occasionally familial, and characterized clinically by retardation of mental development. The brain is of the usual size and weight. The meninges are normal. Throughout all parts of the gray cerebral cortex and rarely in the brain stem, cerebellum, and spinal cord there are firm, white, opaque, spherical or polygonal nodules, 1 mm. to 2 cm. in diameter. They may project on the surface of the hemispheres or into the ventricles. In addition there is at times local hypertrophy of single convolutions. The outstanding microscopic changes within the nodules are loss of neural parenchyma and replacement by dense

glial tissue, and the presence of giant glial and ganglion cells. An accompanying spongioblastoma polare of the striate body or thalamus is a not uncommon finding.

Associated lesions of other tissues include the sebaceous adenoma of the face, the rhabdomyoma of the heart (Farber), and several varieties of neoplasm of the kidney (Moolten). Whether tuberous sclerosis is a developmental anomaly or a true neoplasm is not clear. The syndrome appears more often in the male sex in a ratio of 2 to 1. The course is slowly progressive, and death usually occurs by the twentieth year of life. Epileptic attacks occur at some time in almost all patients.

Familial Ataxia (Friedreich). This is a complex myelopathic and myopathic condition. The spinal cord is small, and the dorsal roots are degenerated. There is a similar loss of both axis cylinders and myelin sheaths in the dorsal columns and in the tract of Lissauer. More frequently there is degeneration of the lateral pyramid and the dorsal spinocerebellar tracts. There are degenerative changes in the ganglion cells of the dorsal horns, less commonly in the ventral horns. The cerebellum shows a wide variety of changes, but in general there is degeneration of the ganglion cells. Marie's cerebellar ataxia is probably the same condition with primary involvement of the cerebellum. Friedreich's ataxia develops within the first few months or years of life, but may be present at birth. There is direct inheritance. The pathologic changes in the central nervous system lead to atrophy of the muscles, ataxia, grossly defective speech, absence of the tendon reflexes, and nystagmus.

Hereditary Spastic Paraplegia and Diplegia (Strümpell). This is a well defined hereditary entity more common in the male sex, characterized by slowly progressive spastic weakness of the legs, and absence of sensory reflexes and psychic changes. Degeneration of the pyramidal tracts and columns of Goll, and sometimes of the spinocerebellar pathways, and loss of Betz cells in the cortex have been observed (Mason and Rienhoff).

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CVII

The Demyelinating Encephalitides

There is a group of diseases of the central nervous system which are characterized principally by demyelination and which are apparently related to one another. Three major disease entities are included—multiple sclerosis, encephalomyelitis, and Schilder's disease—and numerous minor variants.

Pathologic Anatomy. In terms of general pathology the demyelinating encephalitides may be considered either inflammatory or degenerative. The varied interpretation probably depends on the acuteness or chronicity of the reaction. The chief pathologic changes, present in variable degree in any given case, are: focal demyelination particularly perivascularly, slight but not significant degeneration of axis cylinders in the foci, perivascular infiltration with lymphocytes, mononuclear cells, plasma cells, and rare leukocytes, gitter cells and multinucleated cells in the foci, hyalinization of vascular walls and thrombosis, proliferation of glia in the foci, and focal necrosis leading to cyst formation.

Causal Factors. Numerous theories have been proposed to explain the cause and nature of the demyelinating encephalitides. None is entirely satisfactory (Ferraro). The presence of thrombi in the vessels has led some to postulate vascular occlusion as the cause, but most consider it an effect. The demonstration that the urine of patients contains a substance which dissolves myelin is the basis for the lipolytic theory. The occurrence in sequential relation to infectious disease and to poisoning is suggestive of an infectious or toxic origin. However, in the postviral type, it has not been possible to isolate the homologous virus from the brain. The theory which has the strongest support is one concerned with the allergic state.

Relation to Allergy. It was early noted that demyelinating encephalitis followed injection of vaccines and sera, particularly antirabic vac-

cine made from the spinal cord of rabbits. Rivers and Schwenker produced focal demyelination by repeated injection of emulsions of rabbit brain in monkeys. Later, Kabat, Wolf, and Bezer, and Morgan, by combining an adjuvant with the brain tissue, induced more significant lesions after only a few injections.

Interrelation of Disease Entities. Although the disease entities which make up the group of the demyelinating encephalitides have many common morphologic features, there is only limited evidence of transitional forms. A few patients who apparently developed typical multiple sclerosis after an attack of postinfectious encephalitis have been described (Putnam).

Acute Disseminated Encephalomyelitis

Following a number of infectious diseases, notably measles, mumps, smallpox, and chickenpox, and after vaccination for vaccinia and for rabies, a few persons develop a characteristic type of encephalitis. Many terms, e. g., postinfectious encephalitis, acute disseminated encephalomyelitis, and demyelinating encephalitis, have been applied to this syndrome.

Pathologic Anatomy. The brain and spinal cord are swollen and congested. On section the tissue is seen to bulge from beneath the meninges, and there are numerous small petechiae throughout all parts of the brain. Three characteristic lesions are observed microscopically: congestion, perivascular lymphocytic infiltration, and perivascular demyelination. The infiltrating cell is the lymphocyte, although a few polymorphonuclear leukocytes may be present. The cells are confined to the perivascular spaces and rarely invade the nervous tissue. The ganglion cells are in general preserved, and neuronophagia is inconspicuous. With stains for myelin, and

even in ordinary hematoxylin and eosin preparations, small or large zones about the blood vessels show a reticulated structure with loss of myelin. In this area, and particularly about it, there is a moderate number of microglia laden with fat. The astrocytes show no change, and there is no infiltration of lymphocytes into the foci of demyelination. There may be a slight infiltration of lymphocytes in the leptomeninges. These pathologic changes are identical in cases following vaccinia (Turnbull and McIntosh), antirabic vaccination (Bassoe and Grinker), measles (Litvak, Sand, Gibel), mumps (Donohue), and the other infectious diseases.

Clinicopathologic Correlation. The symptoms and signs of involvement of the central nervous system appear usually at the end of the first week of the postinfectious type, and from the eleventh to the thirteenth day of the postvaccinal type, although there are wide variations. There are the usual symptoms of an infection such as fever and headache, together with the signs of involvement of the central nervous system, such as vomiting and paralysis. The mortality rate is about 35 per cent, and in keeping with the absence of change in the ganglion cells, recovery is complete, without residual paralyses (Flexner). The condition occurs in about one out of each 2000 vaccinal vaccinations and in about one in each 4000 antirabic vaccinations.

Multiple Sclerosis

Pathologic Anatomy. The salient pathologic feature of multiple sclerosis is the presence of disseminated islets of sclerosis in the brain and cord and occasionally in the nerve roots, hence the synonyms "disseminated sclerosis" and "insular sclerosis."

On *gross examination* plaques may be felt or seen as gray, waxy or gelatinous, firm, spheroid or ovoid foci, varying from a few millimeters to several centimeters in diameter. The most common sites in the cord are about the glial septa and small vascular channels; and in the brain are in the walls of the ventricular system, particularly the horns of the lateral ventricle and the aqueduct, at the junction of white and gray matter of the cortex and basal ganglia, in marginal zones of the gray matter just beneath the pia, around the blood vessels, and in the optic chiasm and

tract. Most plaques form in the white matter but spread to adjacent gray matter and to other tracts with apparent disregard of all anatomic and functional divisions of the nervous system.

Microscopic examination of an early lesion shows degeneration of myelin and accumulation of gitter cells. There may be slight infiltration of the perivascular spaces with lymphocytes, plasma cells, and rarely polymorphonuclear leukocytes. The vessels within a plaque are essentially normal at this stage. The axis cylinders may be swollen, but are not destroyed. With increasing age of the lesion the fat liberated from the myelin is removed, and astrocytes proliferate to form a dense feltwork of fibroglia. In the most advanced lesions the blood vessels are thickened and hyalinized, and there is fragmentation of the axis cylinders. The leptomeninges in contact with a plaque show fibrous thickening and slight lymphocytic infiltration.

Incidence. The incidence of multiple sclerosis is highest in northern European peoples. In the United States it constitutes 5 to 10 per cent of all "organic nervous diseases and injuries." It is more frequent in men in a ratio of 3:2.

Clinicopathologic Correlation. Symptoms may first appear at any age, but the onset in about 40 per cent is between twenty-one and thirty. The course runs from less than one to over thirty years. Death results from some intercurrent infection, especially of the urinary tract. The characteristic relapses and remissions are probably related to an injury to the axons during demyelination of a plaque.

The mode of onset and the signs and symptoms depend on the location and number of the plaques. Lesions in the spinal cord interrupt the corticospinal tracts, with consequent spastic or ataxic paraplegia, or the spino-cortical tracts, with resultant paresthesia, anesthesia, and loss of reflexes. Plaques in the lumbar cord are related to loss of control of the vesical and rectal sphincters. Foci of demyelination in the internal capsule or in the cerebral peduncles result in hemiplegia, while lesions of the cerebellum cause ataxia, giddiness, and nystagmus. Scotoma, contraction of the visual fields, and derangement of ocular movements are related to plaques in the optic tracts and optic radiation. Total blindness is

rare. The characteristic scanning speech is caused by ataxia of the laryngeal musculature. The slow action tremor probably depends on motor disturbances mediated through the cerebellum. The slight mental deterioration, disturbances of emotional expression, and euphoria are difficult to explain except by postulating involvement of the subcortical radiations.

Schilder's Disease

Pathologic Anatomy. Schilder's disease, or diffuse periaxial encephalitis, is characterized

In others there is proliferation of astrocytes and induration of the part. In all, the oligodendroglia are swollen and conspicuous. Rarely there are hyperemia, hemorrhage, and infiltration with leukocytes. The gray matter and the arcuate fibers are in general normal, although the nerve cells of the cortex may show secondary degeneration from damage to the axons in the white matter.

Clinicopathologic Correlation. The symptoms may appear at any stage. In a rare instance it is familial. Because of the variability and the location of the lesions, the clinico-

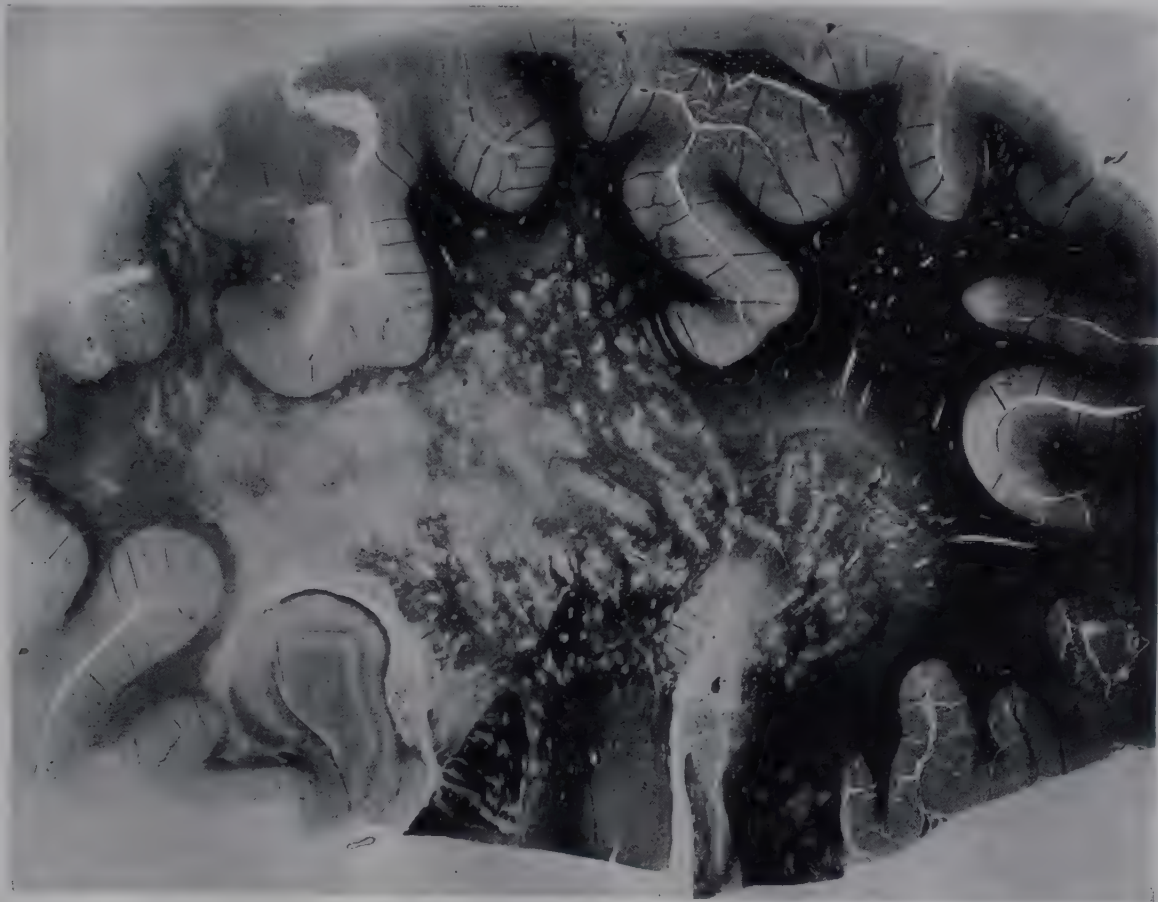


Fig. 457. Brain in Schilder's disease. Foci of demyelination in the white matter of the cerebral hemisphere. (MacCallum.)

pathologically by bilateral, focal destruction of the white matter of the cerebral hemispheres. In the centrum ovale there are foci of demyelination varying in size from a few microns to several centimeters in diameter. These appear to begin about the blood vessels and to spread centrifugally as an expanding sphere.

In the demyelinated parts the axis cylinders vary from normality to complete solution, with tortuous, granular, and swollen intermediate forms. The reaction of the glia is not constant. In some foci there is infiltration of microglia as gitter cells, with removal of the dead tissue and formation of a cavity.

pathologic correlation is difficult. The most constant signs are: blindness, because of the frequent involvement of the occipital lobe; spastic paralysis, related to lesions of the centrum ovale of the temporoparietal lobes; and mental deterioration. The course varies from a few months in the acute type to many years in the chronic type.

Aplasia Axialis of Pelizaeus-Merzbacher. This is a familial condition in which the foci of demyelination are in the corona radiata and corpus callosum. It differs from Schilder's disease in having a strong familial incidence, an onset in infancy, and only minor reduction of mental capacity.

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CVIII

Diseases of the Nervous System of Obscure or Unknown Cause

Although in the past fifty years a great deal of information has been accumulated on the anatomy and physiology of the nervous system, there is still much that is not understood, particularly in the field of psychiatry. The whole subject of nervous disease needs further study and investigation.

Congenital Anomalies

The nervous system is derived from the ectoderm. Early in fetal life the ectoderm in the posterior midline folds in to form the neural tube. The cephalic part becomes the brain and the caudal part the spinal cord. At the junction of the neural tube and ectoderm on each side a separate ectodermal mass forms—the neural crest. Some of these cells remain close to the cord and brain as the sensory ganglia, while others migrate to all parts of the body to become the sympathetic ganglia, the adrenal medulla, the carotid body, the organ of Zuckerkandl, and other specialized cells in the skin (melanophores) and in the intestinal mucosa (cells of Nicolas-Kulchetsky).

Spina Bifida. Myelomeningocele. Pilonidal Cysts. At about the third week of fetal life the neural tube separates from the overlying skin, and mesoblastic tissue is interposed between the skin and the neural tube. From the mesoblastic tissue the spinal meninges, vertebral column, overlying muscles, and fibrous tissue are derived. The vertebral bodies are formed and their arches closed by the end of the eleventh week of fetal life. At this time the spinal cord and the vertebral column are of equal length, but with subsequent growth the column becomes much longer, and the nerves from a corresponding segment of the spinal cord must travel caudally within the canal to reach the appropriate orifice. Failure of fusion of the vertebral lamina results in a condition known as “spina bifida.” In a total of

250 examples of the condition, 5 were found in the cervical region, 22 in the thoracic region, 37 in the lumbar region, and 186 in the sacral region (Walker and Bucy). If there is no protrusion of the meninges or of the cord, but only a slight dimple in the skin, it is known as an “occult spina bifida.” Some of the dimples are superficial and others represent the orifice of sinus tracts lined with squamous epithelium penetrating as far as the dura. These sinus tracts are termed “pilonidal cysts,” despite the fact that only a few of them contain hair. The tortuous and narrow character of the tract predisposes to retention of secretion and bacterial infection.

If a bulbous extension of the meninges passes through the deficient lamina into the subcutaneous tissues, it is designated as a “meningocele”; and if the elements of the spinal cord enter into and end in this sac, it is called a “myelomeningocele” (Buchstein and Love). Myelomeningocele is not infrequently associated with internal hydrocephalus. Under these conditions the greater part of the medulla is within the spinal canal, and the cerebellum rests on and blocks the foramen magnum. Thus the fluid formed within the ventricle is free to pass through the foramina in the roof of the fourth ventricle into the spinal subarachnoid space, but it cannot flow upward over the cerebral hemispheres and be absorbed by the cerebral arachnoid granulations (Russell and Donald).

The most common symptoms are in the urinary tract, and it has been estimated that a considerable percentage of children with enuresis suffer from either an evident or an occult spinal bifida (McCarroll). There may be both motor and sensory disturbances in the lower extremities.

Encephalodysplasia. This term includes all anomalies of the brain.

Anencephaly. This condition is a complete or partial absence of the encephalon. The base of the skull is surmounted by a flattened mass of soft, red, richly vascularized tissue, and the vault of the skull is absent—acrania. The frequently impaired development of the pituitary is probably responsible for the changes in the other endocrine glands (Ch'in):

TABLE 57. WEIGHTS OF ENDOCRINE GLANDS IN ANENCEPHALY

Organ	Normal	Anencephalic
Anterior pituitary....	0.059	0.029
Adrenals.....	6.27	0.43
Thymus.....	9.9	17.8
Thyroid.....	1.9	2.4
Testes.....	0.57	0.18
Ovaries.....	0.23	0.12

Microcephaly. True microcephaly is a condition in which the size of the head is restricted disproportionately to that of the trunk. In most cases the general bodily development is highly impaired, the brain is small, and mentality is conspicuously retarded.

Mongolism. The Mongolian idiot has a small, round head, eyes set obliquely and widely apart, a fat face, a high, narrow palate, and a large tongue. Associated anomalies of the heart are not uncommon. The brain is smaller and less convoluted than normal.

Megalencephaly. Occasionally a large, well proportioned brain is associated with mental deficiency. Abnormalities of the ganglion cells and glia can be demonstrated microscopically.

Encephalocele. A part of the cranial content may project through a defect in the bony wall—*meningocele*, if only the meninges are involved, or *meningo-encephalocele*, if the sac contains both meninges and nervous tissue.

Miscellaneous Faults of Development. In *agyria* there is complete lack of gyral development. Focal *macrogyria* and *microgyria* are self-explanatory terms. *Porencephaly* is a local defect of the cerebral hemispheres so that the ventricles are connected with the subarachnoid space through a funnel-shaped hole, lined by gyri covered by pia (Rezek and Marks).

Miscellaneous Hypoplasia, Aplasia, and Agnesia of Specific Structures. The most

notable focal failures of development involve the corpus callosum, the cerebellum, and some of the nuclei of the third, sixth, and seventh cranial nerves. Agnesia of the corpus callosum is usually asymptomatic.

Myelodysplasia. Total absence of the spinal cord—*amyelia*—is always accompanied by anencephaly, posterior rachischisis, and acrania (de Vries). The spinal ganglia and peripheral nerves may be normally developed. Duplication, *diplomyelia* (Herren and Edwards), and splitting, *diastematomyelia*, of the spinal cord may be symptomless.

Anomalies of Bones Adjacent to the Central Nervous System. The central nervous system is encased in a bony covering—the skull and the vertebral column. The peripheral nerves pass over and under bones of both the trunk and the extremities. Anomalies of these may be reflected in the function of the nervous system.

Cervical Rib. The degree of development of cervical ribs varies from slight enlargement of the costal process of the seventh cervical vertebra to the formation of a complete rib reaching to the manubrium. There are usually no symptoms.

Anomalies of the Vertebra (Ehrenhaft). At transition zones of the vertebral column the vertebrae of one segment may take on the characteristics of the adjacent segment. There are usually no symptoms. In *brevicollis* or the Klippel-Feil syndrome there is a reduction in the number of vertebrae and fusion of those present. In a similar anomaly of the sacrococcygeal vertebrae, the trunk is telescoped into the pelvis.

Anomalies of the Shoulder Girdle. Congenitally high scapula, or *Sprengel's deformity*, is frequently associated with a cervical rib (du Toit). *Cleidocranial dysostosis* consists of aplasia of the clavicle and retarded ossification of the membranous bones of the skull (Krabbe).

Anomalies of the Skull. *Craniofacial dysostosis* is a hereditary condition related to oxycephaly, and characterized by a frontal loss at the site of the anterior fontanelle, a short upper lip, a high-arched nose, and eyes set far apart. *Hypertelorism* is an anomaly in which the eyes are widely separated (Greig). *Oxycephaly* is a deformity of the head, which may be tower-shaped, sway-backed, or wedge-shaped. There is great prominence in the re-

gion of the anterior fontanelle. The condition is produced by premature closure of the suture lines of the skull, and continued growth of the brain, so that the skull gives way at its weakest point—the region of the fontanelles. Increase of intracranial pressure from the growing brain is responsible for the principal signs and symptoms—headache, mental dulness, exophthalmos, papilledema, and occasionally convulsions (King). *Platybasia* is an anomaly of the occipital bone and cervical vertebrae with bulging of the edges of the foramen magnum into the posterior fossa (Craig, Walsh, and Camp).

Neuralgia and Neuritis

Unfortunately the terms “neuralgia” and “neuritis” have come to be a diagnostic wastebasket into which are thrown all obscure complaints. Etymologically *neuralgia* is pain in the nerves and *neuritis* is an inflammation of the nerves.

In interstitial neuritis there is inflammation of the perineurium, epineurium, and endoneurium; while in parenchymatous neuritis there is wallerian degeneration of the fibers. In most actual examples of the disease both types are present.

The causes of neuritis and neuralgia are varied. A degeneration, an inflammation, a neoplasm, trauma, or exposure to a chemical can be demonstrated in many patients. In others there is no apparent cause unless the idea of focal infection is accepted. The most common lesions are sciatica, trigeminal neuralgia, and Bell’s palsy (seventh cranial nerve). Texts on neurology should be consulted for details.

Senile and Presenile Atrophy of the Brain

There are inconstant gross and microscopic changes in the structure of the nervous system with advancing age, varying greatly from person to person. Atrophy of the convolutions, widening of the sulci, loss of ganglion cells, gliosis, and slight internal hydrocephalus have been observed. In many instances the loss of nervous tissue has a direct relation to the presence and the intensity of arteriosclerosis of the cerebral arteries, but this cannot be taken as a generalization. All of the changes

are usually conspicuous in patients who have clinical senile dementia (Crichtley). One of the finest descriptions of senile dementia is given in Swift’s “Gulliver’s Travels,” when he speaks of the inhabitants of the island of Luggnagg:

“When they came to fourscore years . . . they were not only opinionated, peevish, covetous, morose, vain, talkative, but incapable of friendship, and dead to all natural affection, which never descended below their grandchildren. Envy and impotent desires are their prevailing passions. . . . At ninety, they lose their teeth and hair; they have at that age no distinction of taste, but eat and drink whatever they can get, without relish or appetite. . . . In talking, they forget the common appellation of things, and the names of persons, even of those who are their nearest friends and relations. For the same reason, they can never amuse themselves with reading, because their memory will not serve to carry them from the beginning of a sentence to the end; and by this defect they are deprived of the only entertainment whereof they might otherwise be capable.”

There are two types of presenile atrophy of the brain that present a similar clinical picture, with sharply different pathologic alterations. Both begin in late middle life, and consist of a subacute mental involution, with certain localizing signs such as agnosia, apraxia, and aphasia.

Pick’s Lobular Atrophy. Lobes of the brain are atrophic, especially the frontal and temporal lobes. The average weight of the brain is 1000 gm. Other parts are less commonly affected. Microscopic sections show a loss of ganglion cells in the first and second layers of the atrophic gyri. There are loss of the Nissl substance and collection of the neurofibrillae at the periphery of the cell. Within the involved area there are hyperplasia of astrocytes and an increase in the number of microglia.

Alzheimer’s Disease. The brain is diffusely atrophic, with slight thickening of the leptomeninges. Two histologic changes are constant: the formation of senile plaques and disturbances in the neurofibrillae. The plaques vary in size and consist of an acellular mass of argyrophilic substance surrounded by distorted microglial cells and swollen, tortuous nerve fibers (Fig. 458). The changes in the

neurofibrillae are thickening, fragmentation, and final disintegration of the axons. In the ganglion cells a similar change, together with collection of the neurofibrillae at the periphery of the cell, is observed (Leavitt and Lewey).

Landry's Syndrome

Landry's paralysis is a clinical syndrome, not a pathologic entity. It consists of an acute ascending flaccid paralysis of the limbs and

are lost. There is a corresponding degeneration of the axons of the pyramidal tract through the internal capsule, the peduncle, pons, and spinal cord. The loss of cells is greatest in the third and fifth layers of the motor region (Davison). Analogous cellular changes affect certain of the cranial nuclei, notably the seventh, tenth, eleventh, and twelfth; and the motor cells of the anterior horns, particularly in the cervical and lumbar enlargements. In general the lateral gray columns are preserved.

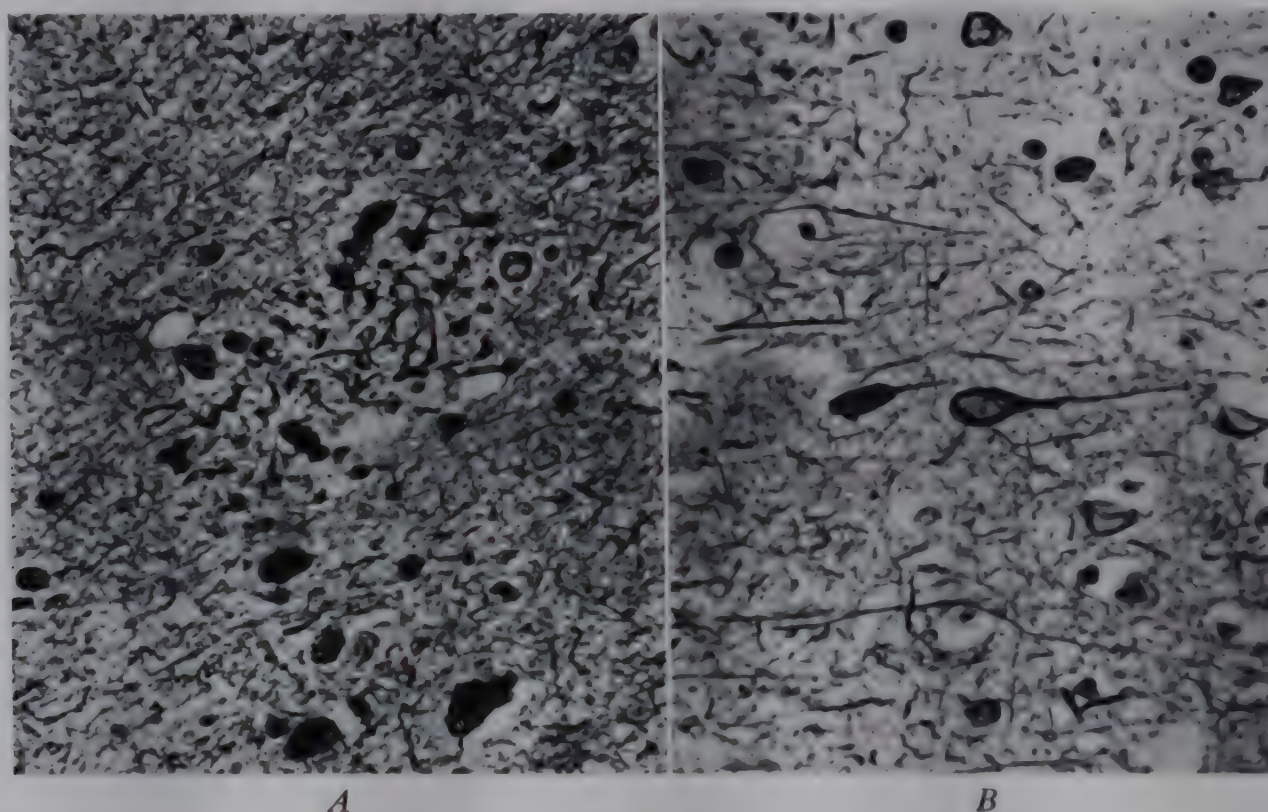


Fig. 458. Alzheimer's disease. *A*, Senile plaque. *B*, Swelling and clumping of neurofibrillae in ganglion cell (Bielschowsky's stain).

trunk, reaching to bulbar levels, with inconspicuous sensory changes and no disturbance in the sphincters. The syndrome may be associated with an acute, ascending type of poliomyelitis, with rabies, or with bacterial disease; and it occasionally follows the administration of a chemical agent such as arsphenamine.

Progressive Spinal Muscular Atrophy. *Amyotrophic Lateral Sclerosis.* *Progressive Bulbar Paralysis*

These three clinical syndromes were originally described as separate clinical and pathologic entities, but further study has shown that they are variants of one pathologic process.

Pathologic Anatomy. The Betz cells of the cerebral cortex undergo atrophy; the Nissl substance disappears; and eventually the cells

There is a corresponding degeneration of the ventral roots and of the peripheral nerves, and frequently there is less change in the nerves than would be expected from the loss of ganglion cells. The earliest muscular changes are in the small muscles of the hands, the interosseous muscles, the lumbricales, and the muscles of the palm forming the thenar and hypothenar eminences. The muscle fibers are small, and the cross-striations are lost. An occasional fiber undergoes hypertrophy. There are moderate interstitial fibrosis and fat infiltration, but no cellular infiltration.

Incidence and Causal Factors. Men are more frequently affected than women in a ratio of 3:1. Direct inheritance is rare. The cause of the primary types of motor neuron disease is unknown.

Clinicopathologic Correlation. If the disease is most advanced in the muscles the patient presents the picture of progressive muscular

atrophy; if in the cord, amyotrophic lateral sclerosis; and if in the medulla, progressive bulbar paralysis. The syndrome of progressive muscular atrophy may be symptomatic or primary. Causes of the symptomatic type are syringomyelia, tabes, syphilis, lead poisoning, and vascular lesions. The onset of the primary type is usually during middle adult life. Loss of the motor neurons leads to paralysis and atrophy of the voluntary muscles. Progression is gradual, until most of the somatic musculature is involved. In order of frequency the earliest groups to show disease are the distal segments of the hands (cervical type), the muscles of chewing, speaking, and swallowing (bulbar type), the distal segments of the feet (lumbar type), and the extra-ocular muscles (ophthalmoplegic type). Mental symptoms are not uncommon. They are probably related to the spread of the cellular lesions in the motor cortex to the adjacent frontal lobes.

Paralysis Agitans

Parkinson's* characterization of the disease named after him was: "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace; the senses and intellects being uninjured."

Types of Parkinsonism. In addition to the agnogenic type of the disease described by Parkinson, there are two symptomatic varieties: one that follows lethargic encephalitis, and the other associated with cerebral arteriosclerosis. In general, lesions of the pallidum are more conspicuous in the agnogenic form, while changes in the substantia nigra are outstanding in the postencephalitic form.

Pathologic Anatomy. The essential pathologic changes are accumulation of fat, atrophy and loss of the ganglion cells, slight cellular infiltration, and neuronophagia in many focal regions of the brain: putamen, caudate nucleus, globus pallidus, substantia nigra, locus caeruleus, corpus luyisi, and the red nucleus.

* James Parkinson (1755-1824) published the "Essay on Shaking Palsy" in 1817, after a study of six victims of which two were "occasionally met within the street" and one "was only seen at a distance."

There is a concomitant loss of fibers in these regions and in the projection systems from them. In the advanced stages there are gliosis and thickening of the blood vessels. This latter change is probably responsible for the miliary foci of perivascular encephalomalacia—cribriform state—occasionally seen in the involved foci.

Causal Factors. Predisposing and exciting causes of the agnogenic type are unknown. The onset in over 40 per cent during the sixth decade excludes senility alone as a major factor. Rarely a hereditary incidence is encountered, suggesting that paralysis agitans belongs in the category of diseases resulting from presenile degeneration of local nuclear and fiber systems.

Clinicopathologic Correlation. The course of paralysis agitans extends over many years, with periods of amelioration or relapse. Death is usually caused by some intercurrent disease. It appears that lesions of the pallidum and reticular portion of the substantia nigra result in rigidity, and that lesions of the zona compacta of the substantia nigra result in the characteristic tremor (Davison).

Syringomyelia

The term "syringomyelia" denotes the formation of a cavity in the cord.

Pathologic Anatomy. The lesion is most frequently found in the cervical region. The involved segments are enlarged and flattened, and on section one or more intercommunicating or detached cavities, filled with a clear, colorless or yellow fluid and limited by white, smooth, firm walls, are seen. The most common site of single cavities is the ventral gray commissure. Cavities are usually lined by dense glial tissue, rarely by connective tissue or ependyma.

Pathogenesis and Causal Factors. In congenital syringomyelia there is apparently a defective closure of the neural tube and derangement of cellular genesis. Acquired syringomyelia is a complication of syphilitic pachymeningitis, multiple sclerosis, trauma, vascular occlusion, and tumors.

Clinicopathologic Correlation. Syringomyelia is seldom seen before the second decade, and it is slightly more common in men. Rarely a hereditary influence is noted. In about 10 per cent there are other congenital anomalies. Im-

pulses for pain and temperature sensibility are carried over the gray commissure, which is the usual site of the cavity; hence there is a segmental loss of the sense of pain and temperature, without loss of tactile sense. Encroachment of the cavity on the ventral and lateral gray horns results in somatic and sympathetic paralysis, and arthropathy of the Charcot type. The loss of the sense of pain and temperature leads to repeated injuries of the fingers, which do not heal normally. The skin becomes dry and thickened, and the subcutaneous tissues are edematous.

Epilepsy

Epilepsy may be defined as a syndrome characterized by paroxysms, of which convulsive movements or loss of consciousness or both are the principal elements.

Pathologic Anatomy. The pathologic changes responsible for this clinical syndrome are extremely varied, and include congenital anomalies of the brain, traumatic lesions, tumors, parasites, syphilis, tuberculosis, an abscess of the brain, meningitis, encephalitis, multiple sclerosis, and various disturbances of the circulation. In none of these pathologic conditions is epilepsy an invariable or even a common occurrence. For example, only 4½ per cent of 25,000 soldiers with wounds of the skull developed epilepsy. It is evident that the clinical symptoms are related to some more subtle disturbance, either anatomic or physiologic, and that they cannot be associated with the diseases listed above. Most epileptics who come to autopsy have suffered from epilepsy for some months or years and have resided in an institution. Most of them have mental deterioration in addition to epilepsy, and changes in the brain cannot be assigned to one or the other of these conditions.

Pathogenesis. There are four theories, all unproved, concerning the pathogenesis of epilepsy: the irritation theory, the release theory, the short-circuit theory, and the explosive theory. Of these the explosive theory, which assumes some sudden change in the physicochemical state of most of the neurons in the central nervous system, is the most cogent. It adequately explains the phenomenon of an aura and the onset of convulsions, and fits in with the known therapeutic procedures that prevent or decrease the number of epileptic

seizures. But whether this mechanism, or any of the others suggested, is the true and only cause of epilepsy must remain for future investigation to determine (Lennox and Cobb).

The Pathology of the Psychoses

It would not be profitable to enter into a full discussion of the pathologic changes in the psychoses. Both degenerative and atrophic changes in cells have been reported, but it is not certain whether they are cause or effect. It is probable that physiologic and chemical studies of the cerebral tissue will yield more significant information than will pure anatomic studies.

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CIX

Tumors of the Central Nervous System—Intracranial Tumors

Intracranial tumors may be classified into five categories: encephalic tumors (gliomas), tumors of the coverings of the nervous system (meningeal fibromas and neurinomas), tumors of the hypophysis and parahypophyseal tissue, tumors of the vascular system, and miscellaneous tumors. The approximate percentage incidence of each group is 45, 20, 10, 2, and 23 respectively.

General Consideration of the Gliomas

For nearly seventy years after Virchow first recognized that certain tumors of the brain

Astroblastoma
Astrocytoma
Oligodendroglioma
Medulloblastoma
Ganglioneuroma
Neuro-epithelioma
Choroidal papilloma

Continued study indicated that most tumors of the brain contain two or more cellular types; in other words, they are in fact composite tumors. With this viewpoint there has been a tendency to group the types in categories and designate the grade by the degree of differentiation. Thus, the glioma with predominant astrocytes becomes glioma grade 1, and the glioma with mostly multiform glial cells is a glioma grade 4.

TABLE 58. INCIDENCE AND DISTRIBUTION OF EIGHT TYPES OF GLIOMA

Tumor	Approximate Percentage of All Gliomas (Cushing)	Average Age in Years	Principal Location	Average Survival Period in Months (Bailey and Cushing)
Glioblastoma multiforme.....	30	40	90% in the cerebrum	12
Spongioblastoma polare.....	5	15	50% in the cerebellum; 30% in the brain stem	46+
Astroblastoma.....	5	35	65% in the cerebrum; 15% in the cerebellum	28+
Astrocytoma.....	37	30	65% in the cerebrum; 25% in the cerebellum	75+
Oligodendroglioma.....	4	35	All in the cerebrum	66+
Medulloblastoma.....	12	12	All in the cerebellum	17
Ependymoma.....	4	25	75% in the fourth ventricle	32+
Pinealoma.....	2	15	All in the pineal	18

were distinctive and arose from the specialized cells of the nervous system, they were known collectively as "gliomas."

Between 1915 and 1930 a number of investigators proposed classifications based on cellular type. Eleven types of glioma became generally recognized:

Glioblastoma multiforme
Spongioblastoma polare
Ependymoma
Pinealoma

If this composite character of brain tumors is recognized, it is still possible to define the eleven types in terms of incidence, appearance, and clinicopathologic correlation.

Incidence and Distribution. Each of the eleven types of glioma has distinctive biological properties. These are summarized in Table 58. Because of the rarity of the ganglioneuroma, the choroidal papilloma, and the neuro-

epithelioma, they are omitted. Sixty per cent of gliomas are in the cerebrum, 23 per cent in the cerebellum, 15 per cent in the cerebello-pontine angle, and 2 per cent in the brain stem. Similar tumors of the spinal cord are rare, but the most common type is the ependymoma (Kernohan). Massive hemorrhage in a brain tumor is occasionally observed (Globus and Sapirstein).

Pathologic Anatomy of the Gliomas

Glioblastoma Multiforme. The neoplastic tissue is swollen, soft, and grayish blue, with

Spongiosoblastoma Polare. The type cell of this tumor is the polar spongioblast, which may be unipolar, bipolar, or multipolar. The presence of the processes, the absence of fibroglia and neuroglia, and the palisading of the cells are characteristic features. Mitotic figures are inconspicuous.

Astroblastoma. The type cell of this tumor is the astroblast, with a characteristic single large expansion attached to blood vessels, or a connective tissue surface, by a foot plate. Hence there is frequently a perivascular radial arrangement of the cells. Multinucleated cells

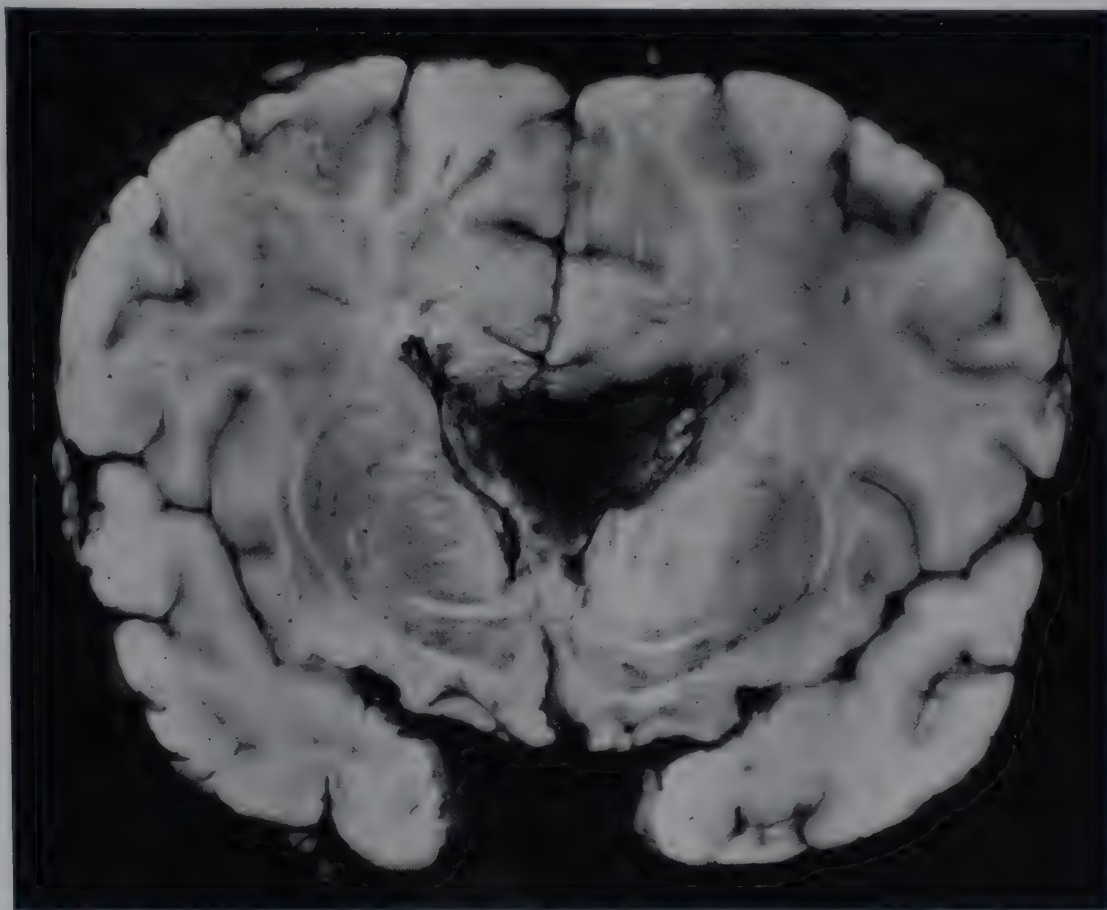


Fig. 459. Glioblastoma multiforme of the corpus callosum.

numerous small and large foci of hemorrhage, necrosis, and cyst formation. The surrounding cerebral substance is pearly gray, translucent, and frequently hemorrhagic. There is great multiformity of cellular types. There are small cells with single hyperchromatic nuclei and scanty cytoplasm, frequently fusiform in shape, and arranged radially about the blood vessels or in parallel rows. Distributed between these cells are more mature astrocytes. Mitoses are abundant. Giant astrocytic forms with single or multiple nuclei are common, especially near the border of the neoplasm. About the smaller blood vessels there are hyperplasia of the adventitial cells, hypertrophy and hyperplasia of the endothelium, and hyalinization of the wall.

are occasionally seen. The leptomeninges may be invaded.

Astrocytoma. The astrocytoma is a firm, white, granular or fibrillar, nonencapsulated tumor. On the basis of the amount of fibrillar material, three types are recognized: pilocytic astrocytoma, gemistocytic astrocytoma, and astrocytoma diffusum. In the first there are many slender neuroglial fibrillae, and cysts filled with a coagulable yellow fluid are often seen. The gemistocytic astrocytoma is characterized by the presence of large, plump astrocytes with a minimum of fibrillae. Cysts are unusual. The astrocytoma diffusum is made up of numerous small hyperchromatic cells, admixed with more immature spongioblasts and a few non-neoplastic ganglion cells.

Oligodendroglioma. As observed with ordinary stains the type cell of this tumor is a small round cell with inconspicuous cytoplasm and a halo about the nucleus. The cells are closely packed and separated into small or large lobules by scattered trabeculae of astrocytes.

characteristically a gray, soft, infiltrating tumor of the roof of the fourth ventricle and the vermiform and lateral lobes of the cerebellum. The meninges are characteristically invaded. Cysts do not form. Implantation metastases into the spinal meninges may frequently be

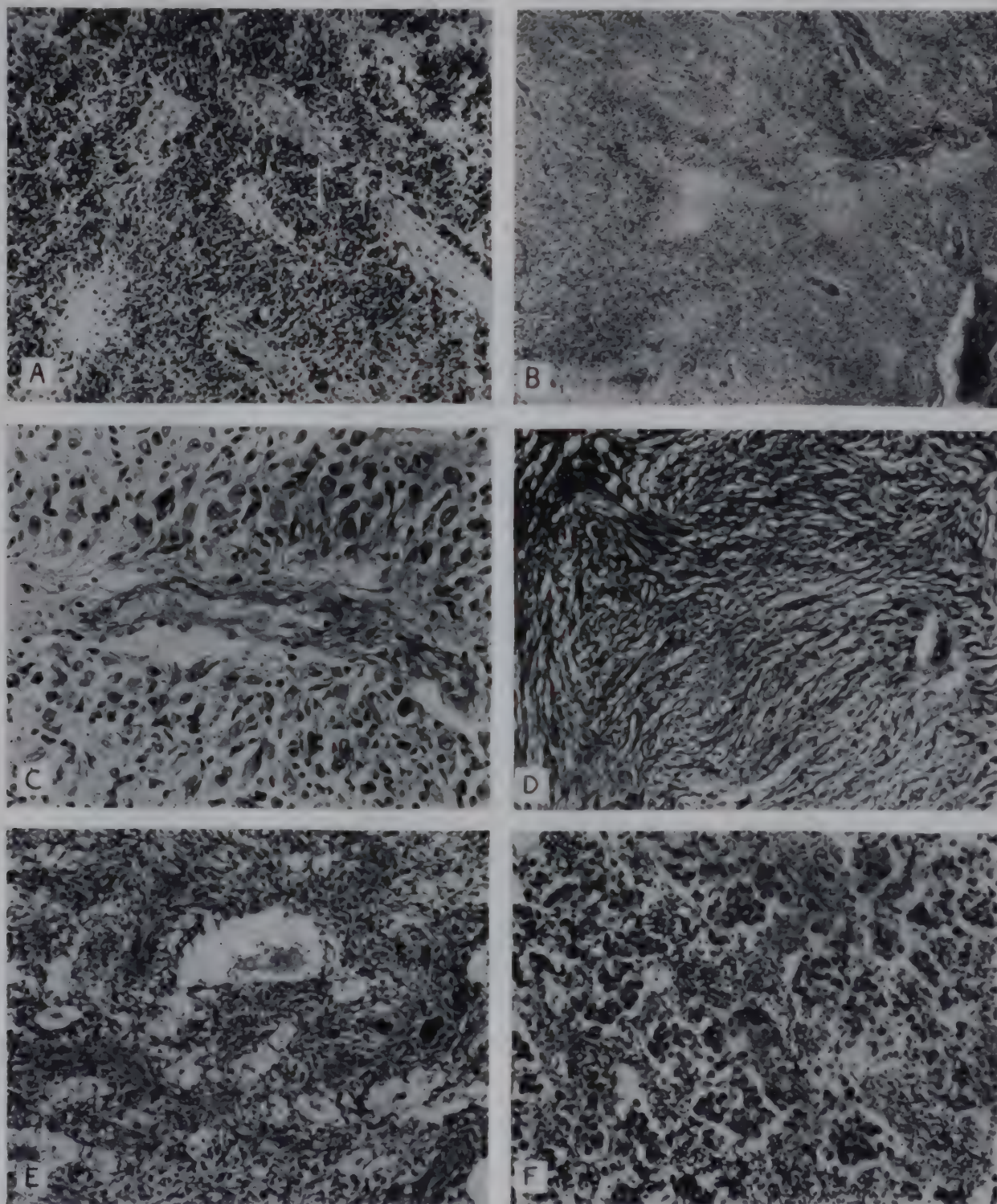


Fig. 460. *A*, Medulloblastoma. The cells are small and hyperchromatic with little stroma between them. *B*, Glioblastoma multiforme, showing irregularly outlined foci of necrosis with palisading of spongioblasts. *C*, Astroblastoma. Note the radial arrangement and palisading of astroblasts about a small capillary. *D*, Polar spongioblastoma. The typical spindle-shaped cells are arranged in interlacing parallel bundles. *E*, Astrocytoma, showing several small cysts. The astrocytes are well differentiated, and have numerous fibrillary processes. *F*, Pinealoma. Note the two types of cells and the tendency to form a mosaic pattern.

With silver stains the cytoplasm is seen to be granular with a few short processes. Calcification is common, and may be of assistance in establishing a diagnosis because of its appearance on a radiograph. Mitoses are frequently seen. The prognosis is usually poor.

Medulloblastoma. The medulloblastoma is

demonstrated. The type cell is small and may be pear-shaped, with a hyperchromatic nucleus surrounded by scant cytoplasm. An occasional cell with a larger, more vesicular nucleus, a prominent nucleolus, and a short process may be present. Mitoses are a constant finding. Careful search will usually reveal in

some parts an arrangement of the cells into pseudorosettes, with the processes of the cells twisted about each other in the center. Occasionally there is a perivascular arrangement. The stroma is composed of connective tissue arranged in broad and narrow trabeculae, carrying thin-walled blood vessels. Metastases in the spinal meninges are observed (Winkelman and Eckel).

Ependymoma. The characteristic cell of the ependymoma has a short process extending into the tissue, and a ciliated surface toward a lumen. In the cytoplasm beneath the luminal surface small blepharoplastic granules may be seen. Between the characteristic, at times glandular, ependymal cells are astrocytes and polar spongioblasts. These neoplasms are moderately vascular; necrosis and calcification are occasionally seen; and mitotic figures are extremely rare.

Pinealoma. A pinealoma is characteristically a small, encapsulated tumor, replacing the pineal body and composed of gray, soft, friable tissue. Occasionally there are invasion of the surrounding structures and rupture into the ventricular system. In the latter instance tumors up to several millimeters in thickness may line the lateral and third ventricles. Rarely there are metastases into the spinal subarachnoidal space. The true pinealoma is composed of two cellular types: a large cell and a small cell. The large cell is round or polygonal, with a relatively large nucleus. The small cell resembles the lymphocyte.

The similarity or possible identity of the pinealoma and the seminoma of the testis has led some to postulate that the pinealoma is actually derived from the primordial germ cells and not the pineal. The known occurrence of teratomas including choriocarcinoma in the pineal region supports this view (Friedman).

Precocious Puberty. In about 25 per cent of all patients less than 15 years of age with a tumor of the pineal body there is precocious puberty. It would appear that this syndrome results from pressure or irritative phenomena on the adjacent hypothalamus, rather than directly from the presence of the tumor (Russell and Sachs).

Ganglioneuroma. The histologic structure of the ganglioneuroma of the central nervous system is the same as that in the peripheral nervous system (see that section, p. 960) (Bailey and Beiser).

Neuro-epithelioma. The type cell of the neuro-epithelioma is a cuboidal or columnar ectodermal cell, resembling that of the primitive neuro-epithelium. The cells run in bands or columns, and may appear in the form of rosettes and loops, and the groups of neoplastic cells are separated by trabeculae of connective tissue.

Choroidal Papilloma. This rare tumor is primary in the fourth ventricle in 50 per cent of instances, and in 35 per cent in the left lateral ventricle. It is most frequent in children. The microscopic structure is that of a typical papilloma with a single layer of columnar cells and a delicate connective tissue framework. Seeding of the neoplastic cells through the cerebrospinal fluid has been reported. Associated cysts of the choroid plexus are common (Posey).

Meningeal Fibroma

Pathologic Anatomy. The meningeal fibroma is a firm, spherical or lobulated tumor attached to the dura and pressing on but not usually adherent to the brain. The tissue is grayish white and fibrillar or coarsely granular. Cysts filled with yellow fluid are occasionally observed. Isolated foci of cartilage, bone, and fat may be encountered. The adjacent calvarium shows resorption, hyperostosis, or no change. Occasionally the neoplastic cells invade the calvarium, and rarely they grow as a palpable tumor in the scalp. Microscopically, spindle-shaped, round, oval, and polyhedral cells are observed, arranged in islands or whorls (Fig. 461, A). Between the cells there are narrow and broad bands of collagen and reticulin fibers. There is an abundant vascular supply. Some of the whorls of cells undergo hyalinization and calcification to form the psammoma body (Cushing and Eisenhardt). Rarely these tumors are malignant and metastasize (Russell and Sachs).

Histogenesis. It was originally thought that these tumors were derived from cells lining the internal surface of the dura—hence the name “dural endothelioma.” Mallory was the first to point out that the type cell was fibroblastic in nature and that it originated from cells of the pacchionian bodies contained in the arachnoid, and only later gained parasitic adherence to the dura—hence his name “arachnoidal fibroblastoma.” This idea is now generally accepted.

Incidence and Distribution. The meningeal fibroma constitutes 10 to 15 per cent of all intracranial neoplasms. The greatest incidence is in the fifth decade, and it is rare before twenty and after sixty. There is a preponderance in women of 6:4. The more important sites, in order of frequency, are: parasagittal region, free convexity of the hemispheres, sphenoidal ridge, olfactory groove, suprasellar region, posterior fossa, and spinal cord. An occasional meningeal fibroma is not attached to the dura, but arises from the arachnoid over

Tumors of the Cranial Nerves

Apart from rare examples of tumors of the second and fifth nerves, the only important neoplasm of the cranial nerves is the neurinoma of the eighth nerve.

Acoustic Neurinoma. The usual neurinoma of the eighth nerve that causes symptoms or brings about the death of the patient is 4 to 7 cm. in diameter and lies in the angle between the petrous pyramid, the tentorium cerebelli, the cerebellum, and the brain stem. The sur-

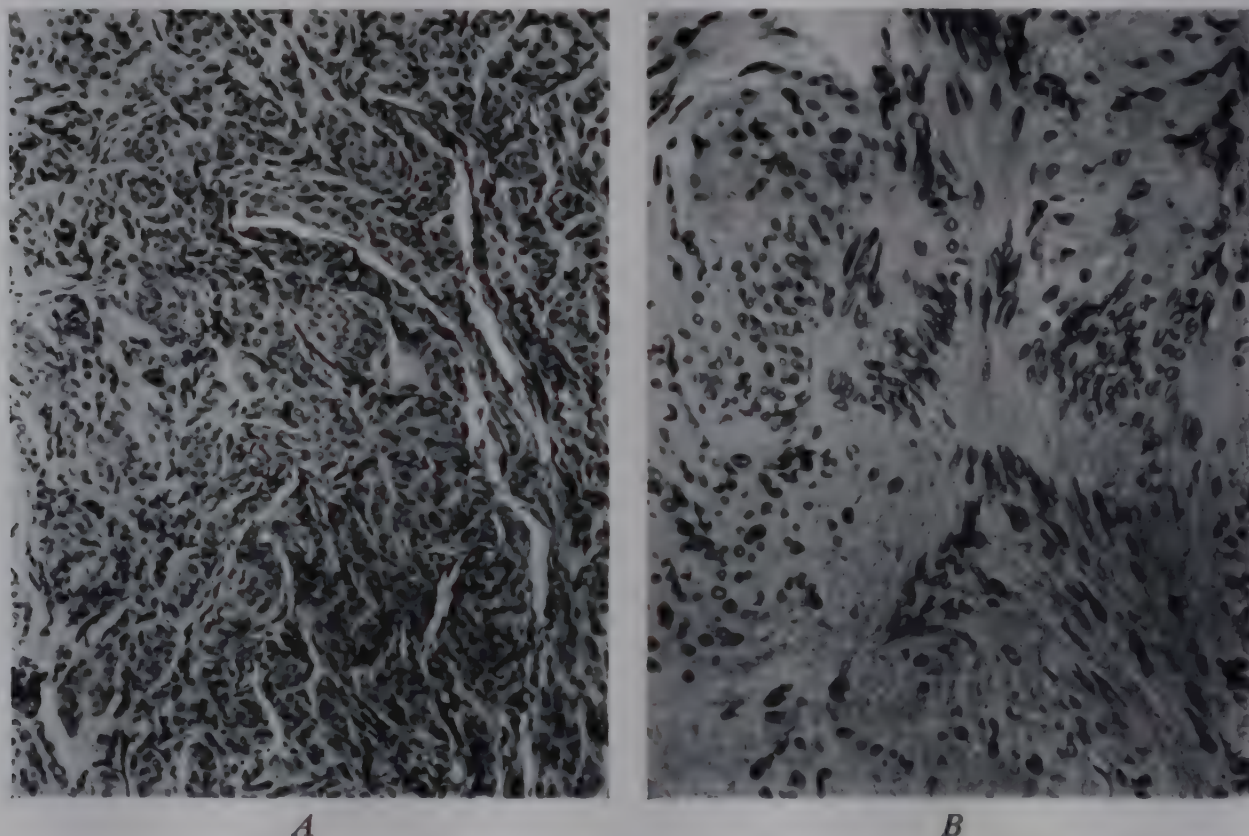


Fig. 461. *A*, Meningeal fibroma showing typical whorls. *B*, Acoustic neurinoma showing the characteristic palisading of nuclei in all fibromas associated with nerves.

the choroid plexus, in the velum interpositum, or in the depths of the sylvian fissure. In a rare patient with von Recklinghausen's disease and bilateral tumor of the eighth nerve there are multiple small meningeal fibromas—a condition known as "meningeomatosis."

Causal Factors. A small percentage of patients give a history of trauma, but it is difficult to establish any relation between the two phenomena. In a significant number, meningeal fibromas are associated with von Recklinghausen's disease.

Clinicopathologic Correlation. There are signs and symptoms resulting from the presence of a space-consuming lesion within the fixed capacity of the cranial cavity, and localizing signs and symptoms related to the site of the tumor.

face is smooth or slightly nodular, and conforms with the shape of the surrounding tissues. The color is pinkish gray, with focal areas of yellow necrosis. Ramifying over the surface are numerous branches of the basilar artery, small veins, and the compressed seventh and fifth nerves. In tumors that extend far caudally, the ninth, tenth, and eleventh nerves may be stretched over the surface. The sixth nerve is usually free. Because of the increased pressure in the posterior cranial fossa there is a characteristic cerebellar pressure-cone. The microscopic structure is similar to that of other neurinomas—spindle-shaped cells frequently arranged in palisades with a moderate amount of intercellular collagen (Fig. 461, *B*).

Histogenesis. Several small tumors have

been studied, and all were on the vestibular division of the eighth nerve within the auditory canal. The difference of opinion concerning the origin of the neoplastic cell—cells of the sheath of Schwann or fibroblasts—is apparently resolved in the case of the acoustic neurinoma because the eighth cranial nerve at the point where this tumor arises has no sheath of Schwann.

Clinicopathologic Correlation. The peak incidence is from thirty to forty-five years. Occa-

tumors from adjacent structures may occur in this area and cause the same syndrome as an acoustic neurinoma.

Tumors of Other Cranial Nerves. Two types of tumor of the optic nerve are worthy of note: the astrocytoma and the meningeal fibroma. The former is a complex mixture of astrocytes and fibroblasts. The latter arises in the sheath of Schwalbe (Davis). Neurinoma of the seventh nerve has been reported (Roberts).

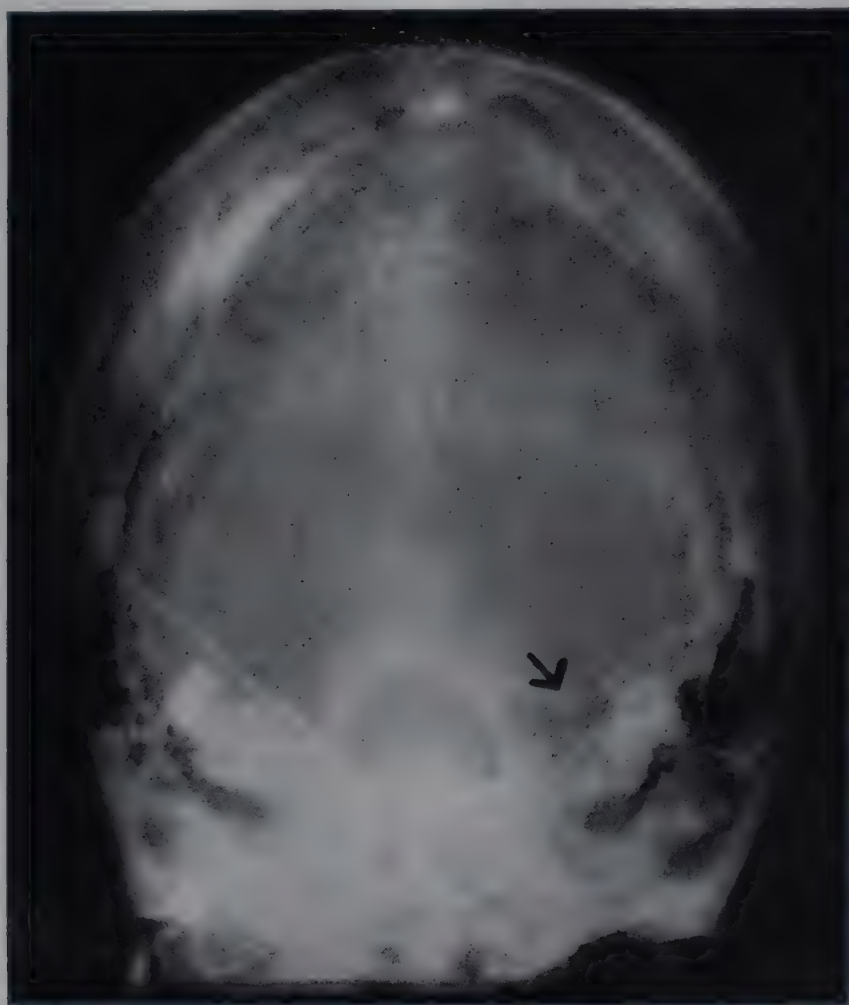


Fig. 462. Absorption of bone about the internal auditory canal with a tumor of the eighth nerve.

sionally the tumors are bilateral and are associated with von Recklinghausen's disease. The symptoms are remarkably constant and are directly related to the pathologic change. Despite the fact that the vestibular branch is involved first, the initial symptoms usually result from pressure on the auditory branch—tinnitus and deafness. Sensory and motor changes from pressure on the fifth, seventh, ninth, tenth, and eleventh cranial nerves appear later. Incoordination is related to pressure on the cerebellum. Erosion of the bone in the canal may be demonstrable in radiographs (Fig. 462) (Revilla).

Tumors of the Cerebellopontine Angle. Gliomas, meningeal fibromas, and extensions of

Tumors of the Blood Vessels of the Meninges—Lindau's Disease

In the literature on this subject there is considerable looseness of terminology, and it is difficult to determine whether or not any given lesion is a true neoplasm. It is probable that most represent congenital anomalies in the formation of the blood vessels.

One of the more interesting conditions is Lindau's disease. In complete form it consists of multiple angiomas of the retina, rhombencephalon, and spinal cord; polycystic disease of the pancreas, liver, and kidneys; cavernous hemangiomas of the liver, and focal hyperplasia of the adrenal cortex and renal tubules.

The angiomas are 10 mm. or more in diameter, and there is a fibrous interstitium between the endothelium-lined channels (Lindau).

Retinal Angiomas. About 20 per cent of all patients with retinal angiomas have one or more of the other lesions of Landau's disease. The remaining 80 per cent are isolated. Hemorrhage into the tumor may occur, and in the process of healing a white scar is formed, termed "Coats' retinitis."

Angiomas of the Skin and of the Meninges. Angiomas of the meninges may be associated

anatomical types are recognized: cranial, vertebral, and sacrococcygeal. It is a well encapsulated tumor, and the soft mucinous or gelatinous neoplastic tissue is divided into lobules by narrow connective tissue septa. Foci of necrosis, hemorrhage, cyst formation, and calcification are uncommon. Infiltration of the surrounding soft tissues is rare, but invasion of the bone occurs in most instances. Microscopic examination shows a mosaic of lightly acidophilic, nonvacuolated, round or polyhedral cells, separated by a small amount of homogenous

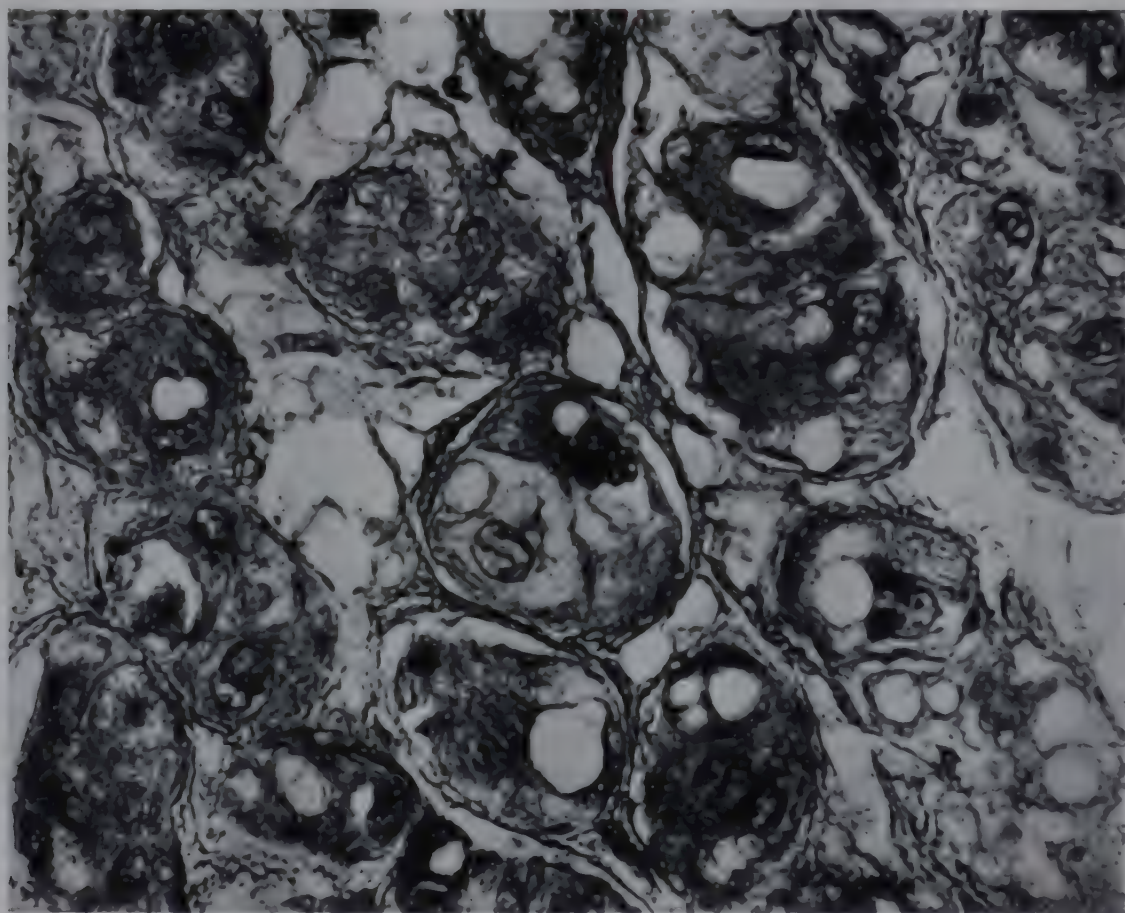


Fig. 463. Chordoma. Note the physaliferous cells characteristic of this tumor.

with angiomas of the skin. The latter are of the capillary type, and frequently follow the distribution of a peripheral nerve. They are designated as "naevus flammeus" (Evans and Evans) or as "Sturge-Weber's disease."

Congenital Telangiectasis and Varicosities of the Vessels of the Brain and Spinal Cord. In contrast with the focal tumorlike lesions described in the preceding paragraphs, foci of the dilatation of large arteries and veins in the leptomeninges are occasionally encountered. They are space-consuming lesions, and the rapid flow of blood produces a bruit (Cushing and Bailey).

Miscellaneous Tumors of the Nervous System and Adjacent Tissues

Chordoma. The chordoma is a tumor derived from remnants of the notochord. Three

intercellular material. In the more completely evolved tumors the cytoplasm is vacuolated and the physaliferous cells are formed. The cytoplasm is rich in glycogen and in mucin (Hass). Chordomas appear at any age from birth onward, but the peak incidence is in middle adult life. A history of trauma is in some instances apparently significant. The cranial type of chordoma forms masses about the clivus, the sella turcica, the nasopharynx, or the dens, hence the signs and symptoms are variable. The sacrococcygeal type rarely surrounds the rectum and causes stenosis.

Teratoma. Intracranial dermoids and teratomas are rare. They occur in the pineal, the third ventricle, the interpeduncular space, the cerebellum, and the region of the sella (Hosoi).

Miscellaneous Tumors. Impingement of

lipomas, myelomas, osteomas, and chloromas on the central nervous system has been discussed in the section on each of these tumors. The paraphyseal cyst is pedunculated into the anterosuperior part of the third ventricle. It causes intermittent, acute, internal hydrocephalus (Weinberger and Boshes).

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Tumors of the Peripheral Nervous System

The peripheral nervous system consists of two parts: nerves, and localized collections of ganglion cells. Nerves consist of axis cylinders, cells of the sheath of Schwann, and scattered fibrocytes and connective tissue. According to the position in the sheath, the latter is designated as "epineurium," "perineurium," and "endoneurium." The cellular elements, for the most part derived from the neural crest, constitute the sympathetic ganglia, the sensory ganglia of the spinal and cranial nerves, and highly developed tissues such as the adrenal medulla, and the carotid body. In addition there are isolated cells in the skin responsible for the formation of pigment, and individual cells in the mucosa of the small and large intestine known as the "cells of Nicolas-Kulchitsky."

Classification. Tumors of these structures may be classified as follows:

1. Tumors of the peripheral nerves
 - A. Neuroma
 - (a) Traumatic neuroma
 - (b) Appendiceal neuroma
 - (c) True neuroma
 - B. Tumors involving nerve terminals
 - (a) Glomus tumors
 - (b) Nevus—malignant melanoma
 - C. Tumors of the nerve sheath
 - (a) Neurinoma—perineurial fibroma
 - (b) Perineurial fibrosarcoma
 - D. Von Recklinghausen's disease
 - E. Miscellaneous
2. Tumors of the cells of the peripheral nervous system
 - A. Ganglioneuroma
 - B. Sympathicoblastoma
 - C. Carcinoid
 - D. Chromaffinoma of the carotid body
 - E. Pheochromocytoma

There is still controversy as to whether the nevus and malignant melanoma are derivatives of the nervous system or epithelium (Lund and Stobbe). They are discussed in the chapter on tumors of the skin (p. 1013).

Neuroma

Tangled and coiled masses of axis cylinders, schwannian syncytium, and fibrous tissue along the course of or on the proximal end of a divided nerve constitute the neuroma.

Traumatic Neuroma. Following amputation, especially of the lower extremities, bulbous masses may develop on the proximal ends of the divided nerves. They should be regarded as reactive hyperplasia rather than true neoplasms. If sensory nerves are included, pain may be severe and reamputation may be required.

Appendiceal Neuroma. In the mucosa and submucosa of the appendix, especially if the lumen is obliterated, small tangled nodules are found, which Masson interprets as neuromas. It has been suggested that they are the cause of chronic or neurogenic appendicitis.

True Neuroma. This is an extremely rare tumor and is probably congenital in the same sense that the capillary hemangioma of the skin is congenital.

Glomic Tumors

Pathologic Anatomy. These peculiar neoplasms are found on the distal parts of the extremities, thus corresponding to the distribution of the normal digital arteriovenous anastomoses of the Sucquet-Hoyer type. They vary from a few millimeters to a centimeter in diameter, and are firm and reddish gray. They are composed of a tangled mass of blood vessels enclosed within a capsule. The blood vessels are lined with a single layer of flattened endothelial cells supported on a delicate fibrous layer. The vascular wall is variable in thickness, and is made up of peculiar cuboid or rounded glomus cells, some of which contain myoglia within their cytoplasm. Each cell is separated from other cells by a delicate net-

work of collagen. With special stains bundles of nerve fibers and individual nerve fibers may be demonstrated in all parts of the neoplasm (Murray and Stout).

pain, paroxysmal and initiated by pressure or cold. The tumors grow slowly and are benign; and removal is spectacularly successful in relieving the symptoms.

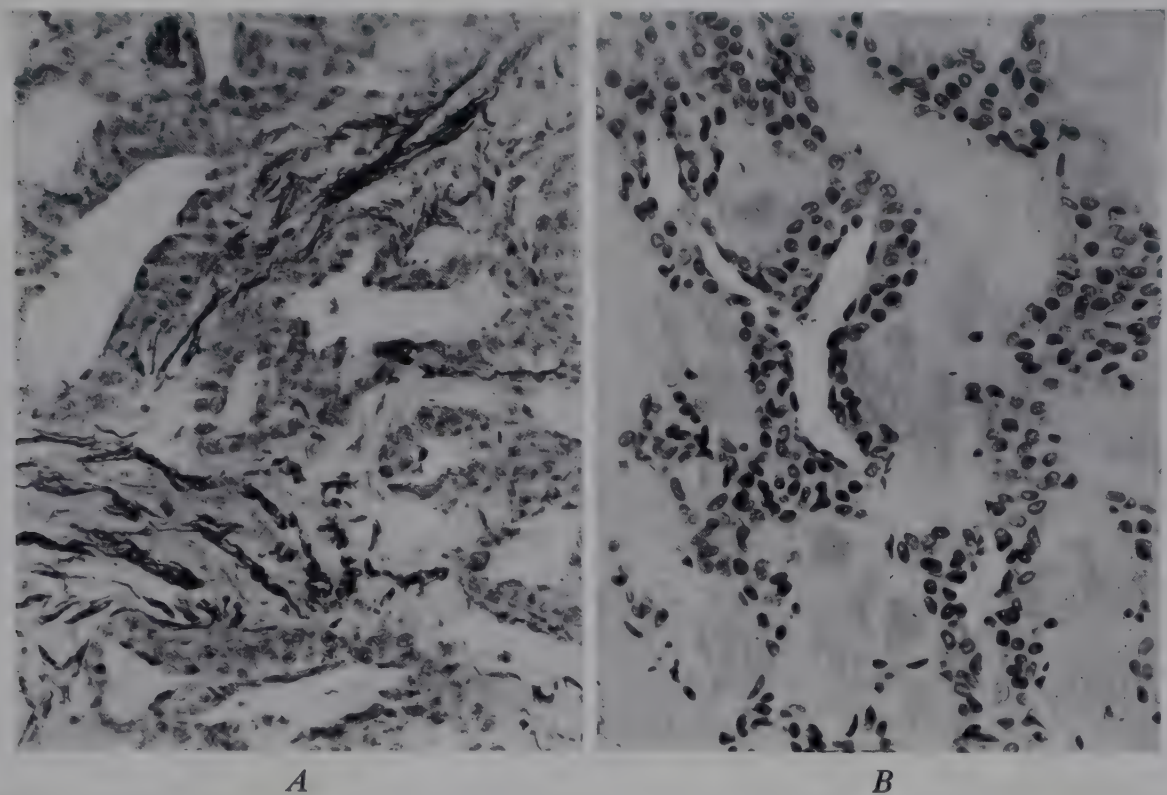


Fig. 464. Glomic tumor. *A*, Note the numerous neurites in the spaces between the glomic vessels (fixed in chloral hydrate and impregnated according to the Cajal method). *B*, Detail of structure. (Photographs by courtesy of Dr. Arthur Purdy Stout.)

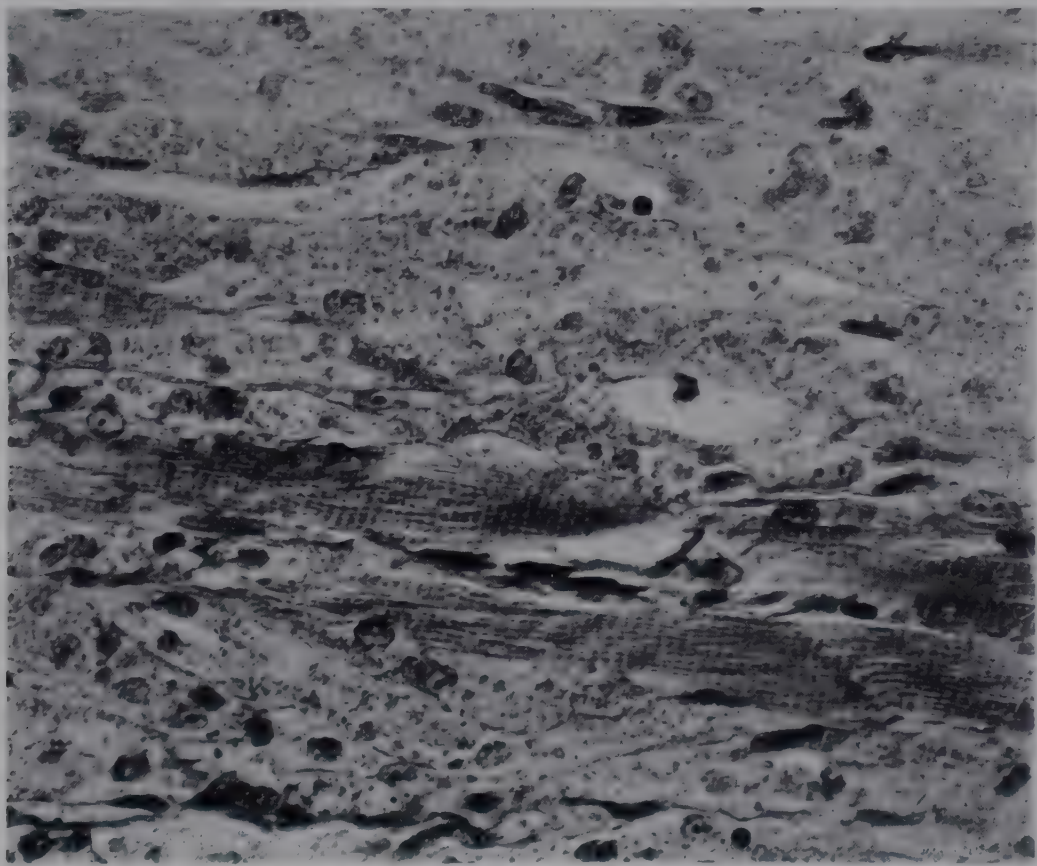


Fig. 465. Granular cell tumor invading skeletal muscle. (Photograph by courtesy of Dr. Arthur Purdy Stout.)

Clinicopathologic Correlation. The sub-ungual type is more common in women, averaging twenty-five years in age; all other types are more common in men, averaging forty years in age. The outstanding symptom, apparently related to the rich nerve supply, is extreme

Neurinoma

This is an encapsulated, firm, fibrillar tumor of the nerves of the extremities and viscera, identical with the more common tumor of the eighth cranial nerve. Many names have

been suggested, but none is entirely satisfactory: neurilemmoma, neurinoma, schwannoma, peripheral glioma, and perineurial fibroma. Two histologic types are recognized, A and B. In type A the cells are spindle-shaped, and are arranged irregularly or in whorls. The nuclei may be arranged in the same plane to give the characteristic palisade appearance. Between the cells there is a small amount of material that stains like collagen. The whorls themselves may be similar to those in the meningioma, and are known as "Verocay bodies," possibly developed from Meissner corpuscles. In type B there is extensive mucoid degeneration. Nerve fibers are found only in the peripheral parts of the tumor.

Pathogenesis. There are two possible cells of origin for the neurinoma: the cells of Schwann, derived from neuro-ectoderm, and the endoneurium, derived from mesoderm. One theory is that since the tumors are composed very largely of collagen, their cells must be derived from the mesodermal elements of the nerve sheath. The other theory is that the rod-shaped cells of the tumor with their anastomosing processes forming a syncytium are more likely the cells of Schwann.

Neurinomas grow slowly and cause pain and paralysis if the larger nerve trunks are implicated. Surgical excision usually effects a complete cure. It is possible that some perineurial fibrosarcomas are derived from the neurinoma (Foot), but this has been denied (Stout, Laidlaw, and Haagensen).

Granular Cell Tumors. Fust and Custer have submitted evidence that the tumor previously designated as granular cell myoblastoma is in fact a neurofibroma. It occurs most frequently in the tongue. The cells are large and have a coarsely granular cytoplasm and small chromatic nuclei.

Perineurial Fibrosarcoma

Pathologic Anatomy. The perineurial or neurogenic fibrosarcoma is primarily a circumscribed and encapsulated, firm, grayish white tumor. Following recurrence it invades surrounding structures and is no longer encapsulated. A connection with a large nerve may or may not be grossly demonstrable. Degenerative changes such as necrosis and hemorrhage are rare. The tumors are composed of elongated cells of spindle shape with long

cytoplasmic end processes. The cells do not form a syncytium but are arranged in bands which interlace; and each cell is separated from the surrounding cells by collagen and reticulum fibers which run with the long axis of the cells. Characteristically the nuclei are arranged in the same plane and give the appearance of palisades. In the more cellular types, giant cells are seen. Neoplastic cells may line vascular spaces. The usual site of metastases is the lung. Invasion of the regional lymph nodes and of other viscera is rare.

Types. There are three clinical types: those observed in patients with neurofibromas or plexiform neuromas of von Recklinghausen, those in patients with the stigmata of von Recklinghausen's disease but free of other tumors, and those not associated with von Recklinghausen's disease. The latter are usually solitary and are located on a major nerve about one of the joints. The gross and microscopic appearance and the clinical course in all these types is essentially the same.

Incidence and Distribution. The highest incidence is between the ages of twenty and fifty, and the two sexes are affected with equal frequency. The most frequently involved *regions* of the body are in order: the knee, groin, upper anterior hip, upper arm, gluteal, upper posterior thigh, scalp, interscapular, upper forearm, and region of the brachial plexus. The most frequently involved *nerves* are in order: ulnar, median, radial, sciatic, femoral, anterior crural, popliteal, lumbosacral plexus, cervical sympathetic chain, and the nerves in the scapular region. Neurogenic sarcomas of the viscera are probably derived from the sympathetic nerves. It is believed by many that all fibrosarcomas with the characteristic whorled structure with palisaded nuclei should be regarded as perineurial fibrosarcoma (Stewart and Copeland).

Histogenesis. There is the same disagreement on the origin of perineurial fibrosarcomas as there is with the neurinoma—fibrous tissue or Schwann cells? Some authors recognize both types on the basis of scant collagen, multinucleated cells, syncytial formation, and many mitoses in the malignant neurinoma. Others deny that a malignant neurinoma has ever been observed.

Clinicopathologic Correlation. The rate of growth is no index of prognosis, but histologic grading is valuable in establishing group prog-

nosis. After local treatment, recurrence is the rule. The outlook is poor except in Grade I slow-growing tumors of the large nerve trunks. Radiation of the usual sort has not proved successful.

Multiple Neurofibromatosis

The entire scope of multiple neurofibromatosis, or von Recklinghausen's disease, is not

tissue. Ulceration is rare. In the dermal and subdermal tissues there is a nonencapsulated nodule of spindle-shaped cells with a moderate amount of intercellular collagen. With special stains numerous nerve fibers and filaments can be demonstrated throughout all parts of the nodule. Similar tumors of the sympathetic nerves in the viscera are observed. The plexiform neuroma of the larger nerves is manifested as an elongation and nodular hyper-



Fig. 466. *A*, Multiple subcutaneous tumors in a woman with von Recklinghausen's disease. *B*, Café au lait spots in the daughter of the patient shown on the left. (Photographs from the files of the Barnard Free Skin and Cancer Hospital.)

yet defined. It is readily acknowledged by everyone that multiple cutaneous neurofibromas, plexiform neuromas, malignant neurogenic fibrosarcomas, elephantiasis neuromatosis, and ganglioneuromas constitute the basic pathologic changes. However the associated lesions in some patients lead into many other fields of pathology: meningeal fibroma, glioma of the brain, tuberous sclerosis, neurinoma of the eighth nerve, multiple lipomas of the subcutaneous tissue, nevi and melanomas of the skin, and congenital angiomas of the skin, eye, and central nervous system. Further study will be necessary to elucidate the relation of these varied pathologic processes.

Pathologic Anatomy. The typical cutaneous neurofibroma of von Recklinghausen is a sessile or pedunculated nodule, soft or elastic, and composed of gray-white, whorled, fibrillar

plasia. The microscopic structure is similar to that of other neuromas. Lesions of the nerves may be extensive, and may be associated with a diffuse overgrowth of tissue in some local area such as the extremities or the scalp—elephantiasis neuromatosa.

Causal Factors. Stigmata. Von Recklinghausen's disease is clearly hereditary as a dominant affecting both sexes and transmitted by both (Turner and Gardner). Careful examination of the skin shows in all cases large and small spots of brown pigmentation—the café au lait spots. In these foci, which are present at birth, there is an increase in the pigment in the basal layer of the epidermis. Not infrequently there are other congenital anomalies such as spina bifida and hypospadias.

Clinicopathologic Correlation. The first cutaneous tumors appear at any time from one

to twenty years of age and steadily increase in size and number with increasing age. The nodule may be directly under a pigmented spot or unrelated to any other change. There is an acceleration in both growth and pigmentation at puberty and during pregnancy. Mental deterioration is not uncommon. Large tumors in the viscera may cause pressure on important structures or obstruction of the hollow viscera. The deformities of the bones—scoliosis and unequal length of the long bones—are attributed to growth of neurofibromas in and

Ganglioneuroma

The ganglioneuroma is most commonly found in the retroperitoneal tissues along the aorta and in the pelvis. Similar tumors are occasionally seen in the mediastinum, in the neck, and in the central nervous system. They are moderately firm and elastic, and vary in size from a few millimeters to many centimeters. There is a distinct capsule, and the neoplastic tissue is glistening, translucent, and yellowish pink, and is divided into lobules by

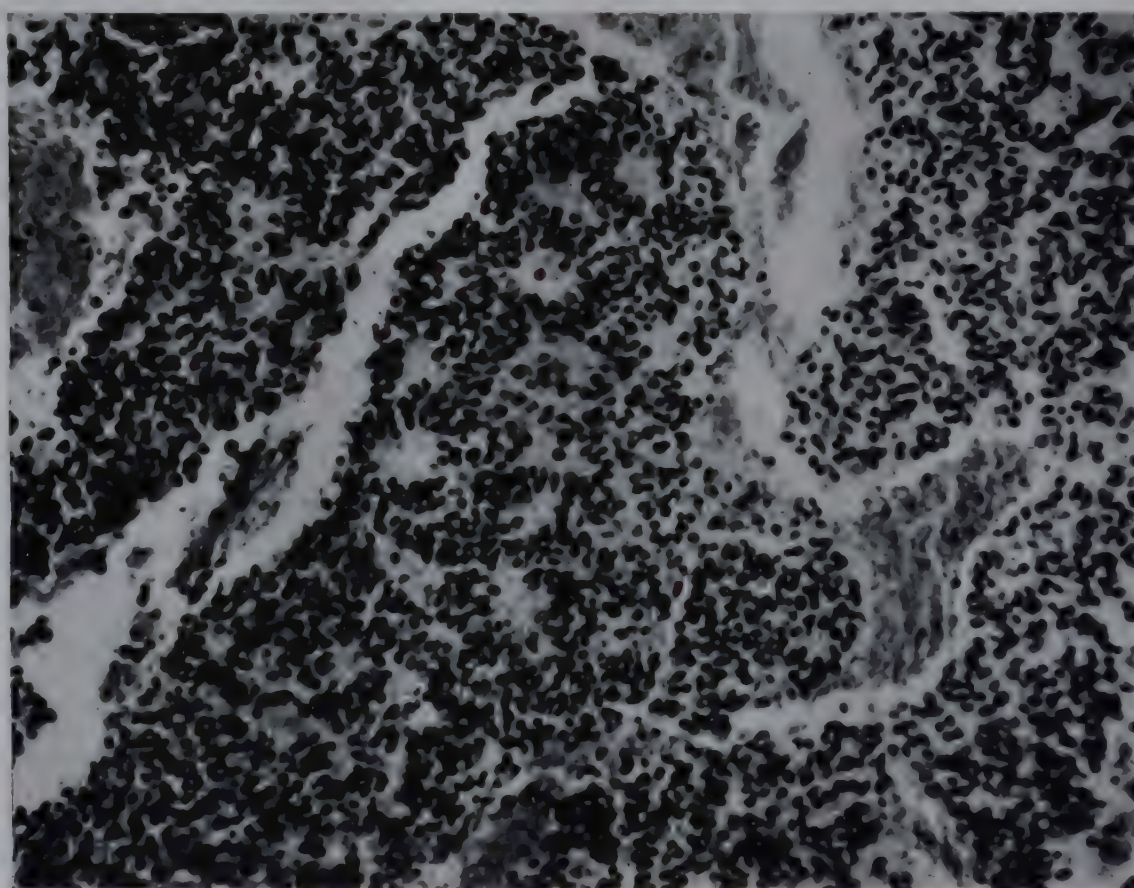


Fig. 467. Neuroblastoma of adrenal. Note rosettes.

about the bones. Hemorrhage or infection in the masses may require surgical intervention. A malignant neurogenic tumor develops at some time in from 10 to 15 per cent of all patients (Penfield and Young).

Miscellaneous Tumors of the Peripheral Nerves

Rare tumors related to the peripheral nerves include the lipoma, the neuro-epithelioma (Stout), and the myxoma. Multiple subcutaneous lipomas are arranged in the distribution of the nerves and are occasionally hereditary (Hellier). Microscopic examination shows irregularly disposed fat cells and congeries of nerve fibers and sheath cells. Congenital papillomas of the skin may follow the course of the peripheral nerves—neuropathic papillomas (Adair and McLean).

connective tissue septa. The microscopic picture is characteristic. There are bundles of nerves embedded in a connective tissue stroma, and numerous ganglion cells with one or more processes and occasionally with two nuclei. The cytoplasm of the ganglion cells contains Nissl substance. Ganglioneuromas are occasionally multiple, or associated with other tumors of the sympathetic nervous system (Wahl and Craig). There is no demonstrable functional activity of the tumors, and the signs and symptoms depend on the formation of a mass with pressure on surrounding structures.

Neuroblastoma

This is characteristically a tumor of infants and children, and with few exceptions is primary in the adrenal gland.

Pathologic Anatomy. The tumor is soft and hemorrhagic. The tissue is white or yellow with necrotic and hemorrhagic foci, and is divided into lobules by fibrous septa. The characteristic cell is small, about the size of a lymphocyte, with a moderately chromatic nucleus and a scant amount of cytoplasm that shows a tendency to flow out into short processes. More careful study of the cell will re-

of the left adrenal is more common in the Hutchison type, and a tumor of the right adrenal in the Pepper type. There is a 5 to 3 preponderance in boys.

Clinicopathologic Correlation. The early signs and symptoms are limited to enlargement of the abdomen because of the presence of a tumor. Later, the metastases and emaciation are prominent. The orbital metastases

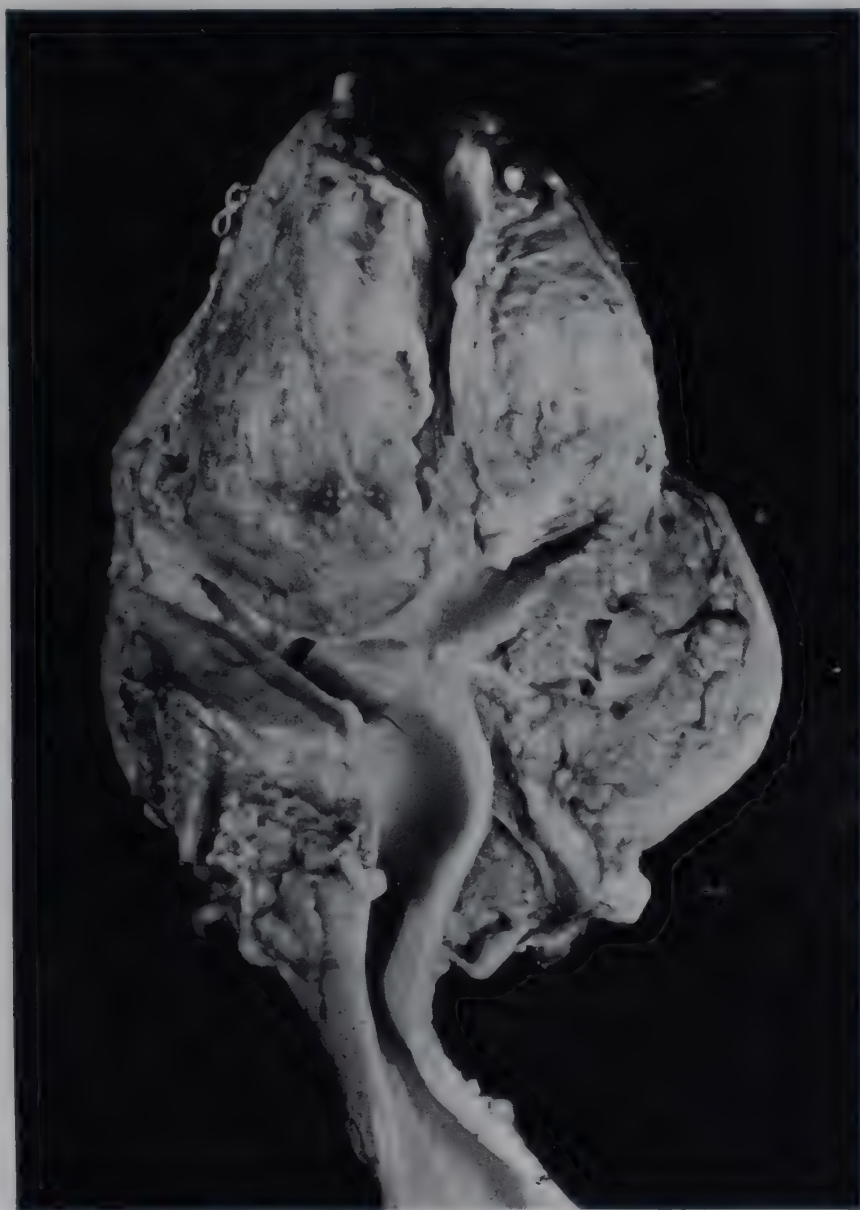


Fig. 468. Tumor of the carotid body. (Goodof, I. I., and Lischer, C. E.: Arch. Path. Vol. 35.)

veal all types seen in the development of the cell of the sympathetic nervous system; and on the basis of preponderance of cellular type, some investigators recognize a sympathogonioma, sympathoblastoma, neuroblastoma, and neurocytoma (Scott and Oliver).

Metastases are widespread, and, on the basis of distribution, two clinical varieties of the disease are recognized: the Pepper type, with conspicuous invasion of the mesenteric nodes and the liver, and the Hutchison type, with large metastases to the skull and periorbital tissues. The right and left adrenal are involved with equal frequency, and about 10 per cent of neuroblastomas are bilateral. A tumor

cause ecchymoses of the lids, exophthalmos, and papilledema. Metastases to the bones, especially in the Hutchison type, result in an anemia. The Pepper type and tumors of the right adrenal are seen more often in younger infants than are the Hutchison type and tumors of the left adrenal. The neoplastic cells are moderately radiosensitive, but there are few five-year survivals with any form of therapy. A child is occasionally born with a large tumor. Willis believes that some examples of Ewing's tumor of bone are in reality metastases of adrenal neuroblastomas.

Neuroblastomas are rarely seen in the retroperitoneal tissues, in the thorax, in the neck,

and in the central nervous system. In adults similar tumors are less malignant.

Carcinoid

The carcinoid is a highly characteristic, bright yellow, nonencapsulated but circumscribed tumor of the mucosa of the appendix and small intestine and rarely of the stomach, colon, and rectum. It is composed of small cuboidal cells, with small spherical and hyperchromatic nuclei growing in groups that resemble a carcinoma invading the lymphatic

impossible to remove the mass without resection of a segment of these vessels. Microscopically the characteristic cell is a polygonal epithelium-like cell, with an abundant acidophilic cytoplasm, containing numerous vacuoles and granules and one or more hyperchromatic nuclei. These cells may be arranged in an alveolar pattern, with narrow or broad fibrous tissue trabeculae between the islands or radially about blood vessels, suggesting a peritheliomatous structure. If the fresh tissue is fixed in the salts of chromium, there may be numerous yellow or brown granules within

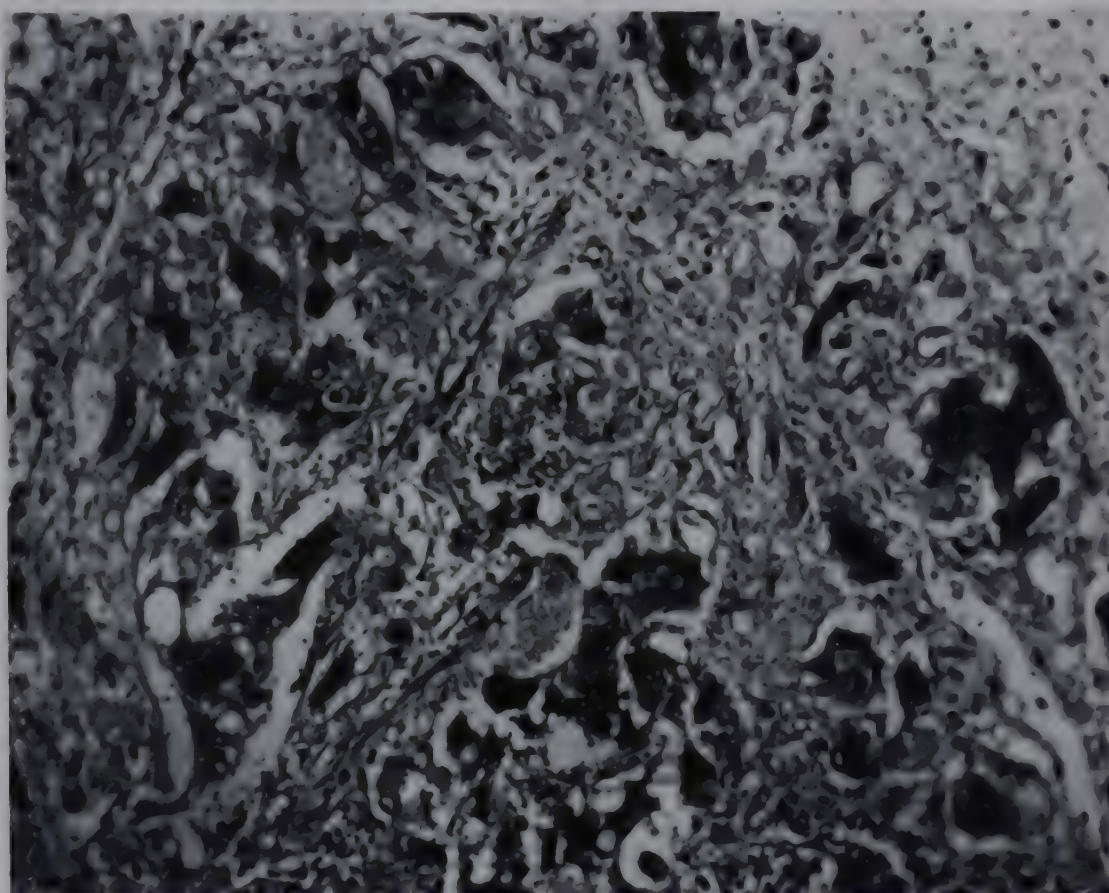


Fig. 469. Pheochromocytoma of adrenal.

channels and nerve sheaths and showing argyrophile granules when properly stained with silver. Metastases to the regional nodes occur in about 10 per cent and to distant organs in less than 1 per cent. Most carcinoids are small and produce no symptoms, but occasionally they grow to large size and obstruct the lumen of the intestine or become ulcerated. They are derived from the cells of Nicolas-Kulchitsky (Gomori; Horn).

Chromaffinoma of the Carotid Body

Pathologic Anatomy. Grossly these tumors appear as reddish brown, lobulated, fairly well encapsulated masses. In many instances the common, internal, and external carotid arteries penetrate through the tumor and it is

the cytoplasm, identifying the cells as chromaffin cells, similar if not identical to those in the adrenal medulla (Goodof and Lischer).

Clinicopathologic Correlation. The principal clinical change is a tumor mass in the neck, coming to the surface under the edge of the sternocleidomastoid muscle in the superior anterior cervical triangle. Because of the incorporation of the carotid artery within these masses they frequently pulsate, and a bruit or thrill is often heard with a stethoscope. As the tumor increases in size, it may press upon important nerves within the neck and give rise to a variety of signs and symptoms—fainting, hoarseness, dyspnea, dysphagia, cough, pain referable to involvement of the cervical plexus, and Horner's syndrome.

Nonchromaffin Paraganglioma of Middle Ear. A somewhat similar tumor occurs in the middle ear, which originates in the glomus jugulare (Lattes and Waltner).

Pheochromocytoma

Pathologic Anatomy. The pheochromocytoma is a characteristic tumor of the adrenal medulla and of the retroperitoneal tissues about the aorta. Because of the marked clinical symptoms they rarely exceed a few centimeters in diameter. They are encapsulated, and are composed of a grayish white, firm, fibrillar tissue. The characteristic cell is a large, polygonal cell, separated from others by a delicate connective tissue framework. The nuclei are small and hyperchromatic, and the cytoplasm is granular and acidophilic. The most characteristic property of the cell is an affinity for chromium salts. After fixation in any solution containing chromium there are numerous fine brown granules throughout the cytoplasm. In the larger tumors there are necrosis and cyst formation (Pinniger and Brown).

Physiologic Aspects and Clinicopathologic Correlation. If the tissue of a pheochromocytoma is examined physiologically it is found to contain significant amounts of epinephrine. This excessive secretion of the hormone is responsible for the pathognomonic clinical sign of paroxysmal hypertension, each attack of which lasts from a few seconds to several hours; and is associated with palpitation, bradycardia or tachycardia, and a sense of uneasiness over the heart. The blood pressure is generally normal between attacks. Surgical removal of the tumor is followed by complete recovery, but a crisis of adrenal insufficiency must be guarded against during the first few postoperative days. It is primarily a disease of adults. Malignant forms of the pheochromocytoma are not physiologically active.

Similar tumors are occasionally found in the thorax. Neoplasms of identical histologic structure in the carotid body and in the organ of Zuckerkandl are inactive physiologically and never malignant.

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CXI

*Diseases of Muscles, Tendons, and Fascias**Primary Muscular Atrophy*

In addition to the atrophy of muscle incident to infectious diseases, nonuse, trauma, and primary diseases of the central and peripheral nervous system, there is a group of rare conditions designated as "primary" or "idiopathic" muscular atrophy. Some of these conditions occur sporadically, and others are hereditary. Some are apparently primary in the muscle and others primary in the spinal cord (Aring and Cobb). The following classification seems the most satisfactory:

Sporadic:

Myopathic:

Congenital amyotonia

Myelopathic:

Progressive muscular atrophy

Amyotrophic lateral sclerosis

Hereditary:

Myopathic

Myasthenia gravis

Familial periodic paralysis

Progressive muscular dystrophy

Congenital myotonia

Myotonic dystrophy

Myelopathic

Infantile muscular atrophy

Hypertrophic neuritis

Peroneal muscular atrophy

Familial ataxia

All except congenital amyotonia have been discussed in Chapter CVI, "Diseases of the Neuromuscular System," and in Chapter CVIII, "Diseases of the Nervous System of Unknown or Obscure Cause."

Congenital Amyotonia (Oppenheim). In this condition all of the muscles of the body are small, but neither gross nor microscopic examination gives any definite evidence that this represents atrophy. It seems much more likely that it is a retardation in the development of the muscles. Signs of the condition

appear during the first twelve months of life. The muscles are flaccid, and those of the leg are the most frequently involved. If death does not occur within a few years, there is usually gradual recovery.

Associated Lesions in Primary Muscular Atrophy. In many of the primary atrophies of muscle there is an associated lesion of the endocrine glands, particularly of the thyroid and the thymus. In most, there is evidence of direct inheritance, either as a dominant or as a recessive. Viewed broadly, it would appear that the primary muscular atrophies represent a complex group of inherited deficiencies, sometimes involving the nervous system, sometimes the muscles, and sometimes the endocrine glands.

The Metabolism of Creatine and Creatinine in Muscular Dystrophies. Normally the animal organism conserves creatine and excretes in the urine a rather constant quantity of creatinine—about 1.5 gm. per day. With atrophy of muscle, creatine appears in the urine, and creatinine decreases in direct proportion to the severity. The injection or the ingestion of creatine or creatinine leads to an almost quantitative excretion of these substances in the urine. The basis for the treatment of the muscular atrophies with glycine is that this substance influences the muscle so that it can better utilize creatine and thus function more effectively.

Myasthenia Gravis

Myasthenia gravis is a chronic disease of adolescent and adult life, characterized by variable weakness of the voluntary muscles, usually first noted in the muscles of the eyes and jaws.

Pathologic Anatomy. The characteristic microscopic lesion is the lymphorrhage, a

focal collection of small lymphocytes about capillaries in the interstitial tissue of the muscle. The muscle fibers are normal. Other organs and tissues, except the thymus, show no consistent change.

Relation to the Thymus. In about one-half of all reported cases of myasthenia gravis, some associated lesion of the thymus, either hypertrophy or a thymoma, has been found (Norris). Several patients have shown remarkable improvement following thymectomy (Blalock, Harvey, Ford, and Lilienthal).

Incidence and Causal Factors. The maximum incidence is between the ages of twenty

flexor tendon of the ring finger. Other nodules form and eventually produce a thick, firm, confluent mass in the palm of the hand, which is adherent to the overlying skin. The tendons, tendon sheaths, and joints are not primarily involved. Microscopic examination shows a mass of fibrous tissue, with foci of lymphocytic infiltration and intertwined nerve fibers. The epidermis is thin and hyperkeratotic. The reticular layer of the corium is replaced by dense fibrous tissue (Kanavel, Koch, and Mason).

Clinicopathologic Correlation. The condition has an insidious onset in middle or late



Fig. 470. Progressive ossifying myositis. (Photograph of specimen from case reported by Opie: J. Med. Research, Vol. 36.)

and thirty-five, and so far as can be determined there is no hereditary influence. The onset is frequently preceded by some infection, but no causal relation has been established. Pregnancy may induce a remission, lasting until the puerperium (Viets, Schwab, and Brazier).

Physiologic Considerations and Clinicopathologic Correlation. The fact that physostigmine, which inhibits the action of cholinesterase, gives temporary relief supports the hypothesis that the patient with myasthenia gravis has an insufficient formation of or an excessively rapid destruction of acetylcholine at the neuromuscular junction (Harvey and Lilienthal). The course is characterized by remissions and relapses. Infection may cause a relapse, and death is frequently unexpected and sudden, from paralysis of the respiratory muscles.

Dupuytren's Contraction

Pathologic Anatomy. The essential pathologic change in Dupuytren's contraction are hyperplasia and contracture of the palmar fascia of the hands. The initial lesion is a nodular thickening, most frequently over the

life, is slowly progressive, involves both hands, the right hand, and the left hand in a ratio of 3:2:1, and has a tendency to appear in the male members of certain families. The contracture and the fixation of the fascia lead to permanent flexion of the fingers and loss of function of the hand. The causal factors are unknown.

Ossifying Myositis

Two types of ossifying myositis are recognized: traumatic and progressive.

Traumatic Ossifying Myositis. In a well developed example of this condition all or a part of an isolated muscle is converted to bone. Microscopic examination shows typical lamellar bone with osteoblasts and osteoclasts in variable numbers, depending on whether the lesion is active or resorbing, respectively. In all instances there is a history of trauma. The initial lesion is a contusion of muscle—a "charley horse"—with hemorrhage and possibly tearing of the adjacent periosteum. After three to four weeks there is beginning ossification. In at least a third of patients there is spontaneous resorption of the newly formed bone in from a few months to a year. In a

few the lesion is progressive, and requires surgical removal (Thorndike) or becomes an osteogenic sarcoma (Pack and Braund).

Progressive Ossifying Myositis. This is a constitutional anomaly of osteogenesis in which there is gradual conversion of the greater part of the musculature of the body into bone: one of the types of "stone man." Serial microscopic studies show degeneration of the muscle fibers, fibrosis, and ossification. In 70 per cent of patients the great toes, thumbs, or both are small, and contain only one phalanx (Opie; van Creveld and Soeters).

Tumors of Muscles, Tendons, and Fascias

The characteristic tumors of skeletal muscle are the rare rhabdomyoma and the rhabdomyosarcoma. Rhabdomyosarcomas are highly malignant and invasive, and recur after surgical removal. They are generally radioreistant (Geschickter). Angiomas (Jenkins and Delaney), lipomas, and chondromas are occasionally seen arising from the interstitial tissue, septa, or fascia about muscles. The giant cell tumors and the synoviomias of tendons are identical with those in the bones and joints respectively (Charache). The tumor designated as granular cell myoblastoma is probably a neurofibroma (see p. 958).

Fibroma of Musculo-aponeurotic Structures. The characteristic fibroma of musculo-aponeurotic structures is usually known as a "desmoid tumor." These tumors are commonest in the abdominal wall. The tumor is a dense, white, firm interlacing mass of fibrillar tissue, with central foci of softening and liquefaction. The tumor is composed essentially of moderately cellular fibroblasts with a slight to moderate amount of collagen. At the edge there is distinct infiltration into the surrounding muscle.

In most patients with desmoid tumor there is a history of trauma, either direct or indirect from stretching of the abdominal wall during pregnancy (Pearman and Mayo).

Miscellaneous Diseases

Ganglion. A ganglion is a cystic swelling, usually in close proximity to a joint or tendon sheath, containing a thick, mucinous fluid. It is surrounded by a dense connective-tissue capsule, but only in rare instances actually communicates with the tendon sheath or the

joint space. There is hyaline and mucoid degeneration of the connective tissue of the capsule. These findings indicate that ganglions are the result of mucoid degeneration of collagen. There is no record of neoplasm arising in a ganglion (Carp and Stout).

Ainhum. Ainhum is characterized by a constriction of the little toe at the digitopltar fold. In the United States it is almost exclusively a disease of Negroes. There are acanthosis and hyperkeratosis of the epidermis, and fibrosis of the dermis. At the line of constriction the cleft is lined by granulation tissue containing numerous foreign-body giant cells. There is atrophy of the underlying bone. The cause is unknown (Spinzig).

Ingrowing Toenail. This is commonest on the outside of the great toe. As the result of wearing ill-fitting shoes, or of improper trimming of the nails, the nail is pushed outward and downward into the soft tissue at the side. The nail becomes thicker and curved. Pressure of the nail forms an ulcer that becomes secondarily infected—perionychia. The infection may spread to the matrix—onychia (Graham).

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CXII

Diseases of the Joints

Diseases of the joints and muscles, collectively known to the laity as "rheumatism," are the most common of all chronic diseases. They are second only to nervous and mental diseases as a cause of absence from work.

rheumatic fever, traumatism of the joints, neurogenic arthropathy, and gout have been discussed. In addition, pathologic changes in the joints in acromegaly, disseminated lupus erythematosus, erythema multiforme, erythema

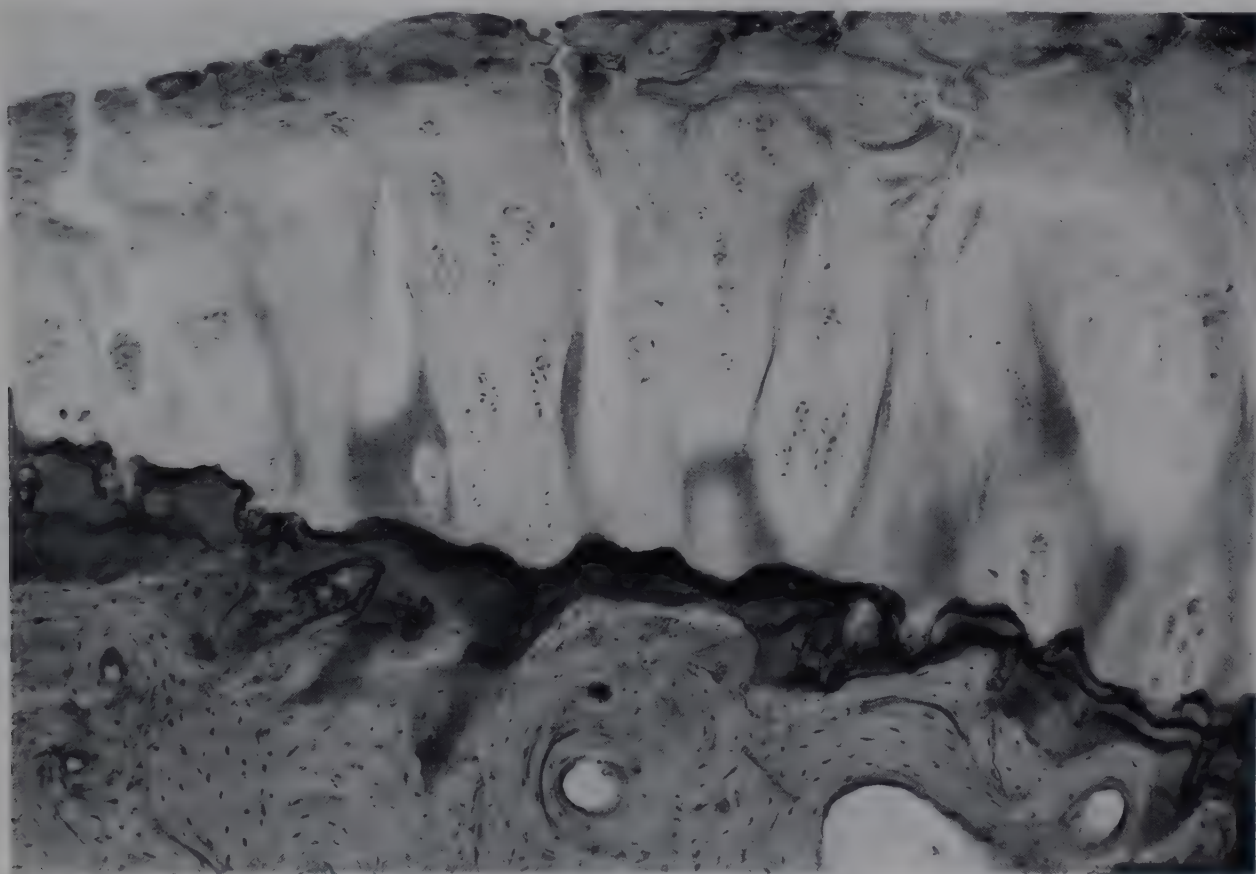


Fig. 471. Degenerative joint disease. Note the fraying of the articular cartilage. (Armed Forces Institute of Pathology, Neg. No. 73809.)

Classification. A satisfactory classification of diseases of the joints is that prepared by a Committee of the American Rheumatism Association (Jordan and others):

1. Infectious arthritis
2. Arthritis of rheumatic fever
3. Rheumatoid arthritis
4. Traumatic arthritis
5. Neurogenic arthropathy
6. Gout
7. Degenerative joint disease
8. Intermittent hydrarthrosis

nodosum, hemophilia, osteochondritis dissecans, and serum sickness have been noted in the sections devoted to those diseases.

Involuntary Changes in the Articular Cartilages—Degenerative Joint Disease

Degenerative joint disease, known also as "hypertrophic arthritis" and "osteo-arthritis," is a disease of late adult life, most pronounced in the weight-bearing joints. The initial lesions appear before the age of forty, and all

In preceding chapters infectious arthritis,

persons of seventy years or more show some evidence of the condition (Bennett, Waine and Bauer).

Pathologic Anatomy. The earliest change is a focal lesion of the articular cartilage, which becomes dull, finely granular, and soft. The lesion is more common in the central parts of the articular surface. Microscopic examination shows that the superficial layers of the cartilage tend to peel off, and that the deeper layers are perpendicularly frayed into parallel

Causal Factors. Most of the evidence points to the wear and tear of life as the true causal factor in degenerative joint disease. Since cases occur in young persons, and affect joints not subjected to stress or trauma, there may be other factors.

Clinicopathologic Correlation. Degenerative joint disease may exist without symptoms. The irregular loss of articular cartilage results in slight malalignment of the joints, and the lipping is responsible for the slight fusiform

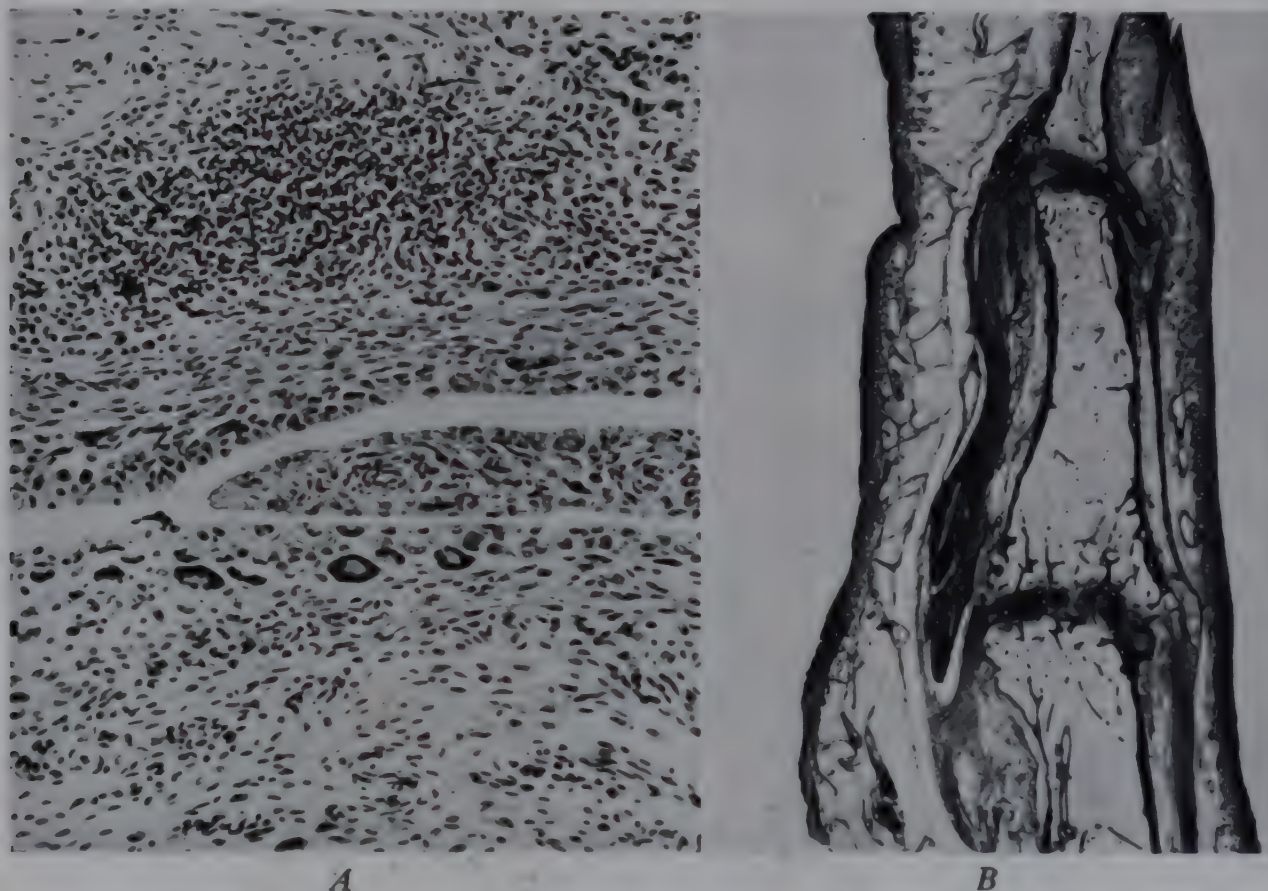


Fig. 472. *A*, Rheumatoid arthritis. Note fibrosis, giant cells, and lymphoid follicle in synovial tissue. *B*, Rheumatoid arthritis. The two interphalangeal joints of the finger show fibrous and bony ankylosis. There is conspicuous osteoporosis of the bones. (Slide by courtesy of Dr. Granville Bennett.)

columns. Some cartilage cells are necrotic, while others multiply and give an irregular cellular pattern.

Trauma in movement causes the soft, partially necrotic cartilage to be destroyed, and the subchondral bone is exposed. Before this occurs, there are proliferation of the osteoblasts, formation of new trabeculae, narrowing of the haversian canals, thickening of the subcortical trabeculae, and invasion of the cartilage by bone.

Concomitantly the cartilage and bone at the margin of the joints proliferate in focal regions to form extensions of the joint surface, variously termed "osteophytes," "marginal lipping," or "hypertrophy." About the terminal interphalangeal joints they form one of the most characteristic lesions of degenerative joint disease: Heberden's nodes (Stecher).

enlargement and limitation of motion. The cause of the pain is not known.

Rheumatoid Arthritis

Rheumatoid arthritis (proliferative arthritis, atrophic arthritis, chronic infectious arthritis) is a chronic progressive disease, characterized early by transient pain and stiffness and swelling of the joints, and late by deformities and ankylosis. Still's disease, Felty's syndrome, the Marie-Strümpell type of arthritis, and the arthritis of psoriasis should be regarded as special types of rheumatoid arthritis.

Pathologic Anatomy. In the early stages there is periarticular swelling and edema, with no conspicuous increase in the amount of synovial fluid and little inflammation of the synovia. This is followed rapidly by prolifera-

tion of the synovial cells to form a thickened synovial membrane or projections into the cavity of the joint, known as villi. At this stage the synovial fluid is increased in amount, and the cartilage loses luster and becomes superficially ulcerated. The increase of synovial tissue eventually covers the entire articular surface and fills the cavity, so that there is fibrous

erative changes in adjacent muscle fibers (Steiner and Chason).

Relation to Rheumatic Fever and to Disease of the Heart. In about 15 per cent of patients with rheumatoid arthritis there are subcutaneous nodules that have a histologic structure similar to the nodules of rheumatic fever. In the tissues about the joint and in the sub-



Fig. 473. Marie-Strümpell arthritis of spine.

ankylosis of the joint. Microscopic examination discloses an edematous, richly vascularized, connective tissue, infiltrated with lymphocytes. Throughout the tissue there are lymphoid follicles, giant cells, and small clefts lined by cuboidal synovial cells (Nichols and Richardson; Steinberg). As the disease progresses there is gradual dissolution of the articular cartilage and invasion of the fibrous pannus by bone. Eventually the trabeculae of bone from the two sides unite and there is bony ankylosis. In the skeletal muscle there are focal accumulations of lymphocytes and plasma cells without fibrosis, but with degen-

cutaneous nodules structures similar to the Aschoff bodies are occasionally seen. Lesions of the heart identical with those of rheumatic fever are observed in a significant number (Baggenstoss and Rosenberg).

Incidence. Over 80 per cent of patients with rheumatoid arthritis are between twenty and fifty years of age, and a family history of rheumatic fever or rheumatoid arthritis is often secured. It is distinctly a disease of temperate climates, as is rheumatic fever.

Causal Factors. In spite of an immense amount of investigation, the cause of rheumatoid arthritis remains unknown. The clini-

cally observed fever, tachycardia, leukocytosis, and increased sedimentation rate, and the histologic evidence of inflammation, point toward an infectious agent as the cause; but no bacterium or virus has been isolated consistently. The remissions during pregnancy and in acute diseases of the liver suggest a relation to some ketosteroid hormone. The remarkable success in treatment with cortisone and adrenocorticotrophic hormone supports this idea.

Clinicopathologic Correlation. The onset of rheumatoid arthritis may be acute, subacute,



Fig. 474. A mechanism of injury commonly resulting in tear of the internal semilunar cartilage. Note abduction of knee and external rotation of foot. (Shands: Handbook of Orthopedic Surgery. C. V. Mosby Company.)

or insidious. The inflammation of the joints leads to local swelling, redness, and pain. The systemic signs and symptoms are those of infection. The disease usually progresses centripetally, affecting the proximal interphalangeal joints first. The terminal interphalangeal joints are commonly spared. The metacarpal, phalangeal, carpal, knee, elbow, ankle, shoulder, and hip joints are affected in that order. The fibrous and bony ankyloses limit motion, which results in a nonuse atrophy of the muscles and an exaggeration of the prominence of the joints. The course is marked by remissions and relapses over many years.

Marie-Strümpell Arthritis of the Spine. In contrast with rheumatoid arthritis of other joints, this type shows a sex preponderance of 9 to 1 in men. There is ankylosis of the vertebrae by fusion of the osteophytes of the adjacent bodies (Fig. 473). The lesions are more common on the right side than on the left in right-handed persons, suggesting a relation to trauma.

Still's Disease. The combination of rheumatoid arthritis and enlargement of the lymph nodes and spleen in children is known as Still's disease. The two latter organs show only a nonspecific type of hyperplasia (Atkinson).

Association with Psoriasis. About 3 per cent of all patients with rheumatoid arthritis have psoriasis. The relation between the two is not clear, but the pathologic changes in the joints in these patients are identical with those in the ordinary type of rheumatoid arthritis.

Felty's Syndrome. This is a symptom complex consisting of chronic rheumatoid arthritis, splenomegaly, and leukopenia. The spleen shows dilated sinusoids, hyperplasia of reticulum cells, and infiltration with plasma cells. The changes in the joints are characteristic of rheumatoid arthritis. The bone marrow is cellular (Curtis and Pollard).

Injury to the Semilunar Cartilages of the Knee Joint

Displacement and tears of the semilunar cartilages constitute the most common disease of the knee. The internal cartilage is more frequently injured, following sudden internal rotation of the femur upon the fixed tibia while the knee is abducted and flexed. The cartilage may be torn or completely loosened from its peripheral attachments. In some instances the displacement recurs frequently and is accompanied by edema of the tissues, increase of fluid in the joint, and extreme pain from locking of the cartilage between the two articular surfaces.

Cysts of the semilunar cartilages filled with soft gelatinous material and lined by flattened cells are not uncommon, and are usually in the external cartilage.

Tumors of the Tendon Sheaths, Joints, and Bursae

Synovioma. There is one distinctive tumor of joints—the synovioma. The tumor is grossly

circumscribed by a pseudocapsule of compressed surrounding tissue about but not in the joints. The neoplastic tissue is soft and pinkish gray with yellow foci of necrosis and red foci of hemorrhage. In removal points of attachment to tendon and tendon sheaths suggest origin in tissue other than joints. The architectural and cytologic pattern is extremely variable. The cells vary from epithelial-like to round or polygonal and typically are arranged in three patterns—about slit-like spaces, in tufts, or as an epithelial structure with a supporting stroma (Bennett).

Although the synovioma may remain localized for a long time, it is definitely malignant. Recurrence and metastases are the rule unless adequately treated.

Miscellaneous Tumors. Other tumors of joints, tendons, and bursae include the giant cell tumor (Geschickter and Lewis), xanthoma (DeSanto and Wilson), and pigmented villonodular synovitis (Jaffe, Lichtenstein, and Sutro).

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CXIII

Diseases of Bone

For a clear understanding of diseases of bone it is necessary to begin with a discussion of osteogenesis. In the first month of fetal life the mesoderm condenses in certain areas to form a model of each of the bones. By the second month ossification has started in most of the larger bones. Final ossification in some bones is preceded by the formation of cartilage—endochondral bone—while in others there is a direct conversion of mesenchyme to bone—membrane bone. Some short bones and the flat bones form from primary centers of ossification, while the larger bones represent the confluence of several areas of ossification. Each center appears at a definite time, and unifies with the others at a certain predictable age. By a study of the bones it is thus possible to estimate age—an important point in medicolegal investigations.

Deformities of the Extremities

Congenital Dislocation of the Hip. There are three anatomic abnormalities in congenital dislocation of the hip: unusual obliquity of the acetabular roof, annular constriction of the abnormally elongated capsule, and anteversion or antetorsion of the femoral neck. The appearance of the upper femoral epiphysis is delayed, and it is smaller than normal. The shaft of the femur is of normal length. The displacement of the head is usually in a cephalad and posterior direction.

Talipes. The term “talipes” is used to designate any deformity of the foot. The modifying adjectives indicate the position: “equinus,” plantar flexion; “calcaneus,” dorsiflexion; “varus,” inversion; and “valgus,” eversion. The most common (75 per cent of all) is talipes equinovarus, better known as “club foot.” Hereditary factors and anomalous development are responsible for the congenital

type. An acquired type is dependent on paralysis of the peroneal muscles. Many secondary changes occur in the tendons, bursae, and bones. Talipes cavus, or “claw foot,” is characterized by an abnormally high longitudinal arch, a depression of the metatarsal arch, and dorsal contraction of the toes. It may be familial, or may follow the wearing of high-heeled shoes, excessive use of the leg muscles, as in professional dancers, or poliomyelitis or other diseases of the central nervous system.

Clubhand. The most common type is seen in congenital absence of the radius, smallness or absence of the thumb, and bowing of the ulna with a lateral convexity.

Syndactylism. Webbing of the fingers is more common than webbing of the toes, and may involve all or only one interdigital space. The union is usually formed by skin and connective tissue, but bone may be present. It is sometimes familial and associated with polydactylism.

Arachnodactyly. There are long, thin, “spider-like” digits associated with anomalies of the eye, skeleton, cardiovascular system and external ear (Ross).

Variation in the Angle of the Femoral Neck. The neck of the femur is normally set at an angle of 130 degrees to the shaft. If it is less the term used to describe it is “coxa vara” and if it is more, “coxa valga.” Both conditions may be congenital or acquired. Causal factors of the acquired type are rickets, osteitis deformans, and infections of the bone or joint.

Variations in the Angle of the Knee. “Genu varum” (bowleg) and “genu valgum” (knock knee) are usually the result of rickets or of a lesion of the tibial tubercles (Barber).

Flatfoot. The basic pathologic change of flatfoot is weakness and relaxation of the ligaments of the longitudinal arch. The tarsal bones are rearranged, the plantar, flexor, and

adductor muscles become atrophic, the lateral muscles are short, and there is a persistent eversion of the foot during periods of weight bearing. Other types of flatfoot are observed in children with genu valgum and with spasm of the peroneal muscles.

Variations in the Angle of the Toes and Fingers. "Hallux valgus" is a lateral angulation of the great toe at the metatarsophalangeal joint. "Hammer toe" is characterized by dorsiflexion of the metatarsophalangeal joint and plantar flexion at the interphalangeal joint, and is most common in the second toe. Both these deformities are caused by pressure from short shoes. The "baseball finger" is the result of sudden, forceful flexion of the distal phalanx, with avulsion of the insertion of the extensor tendon.

Exostoses on Bones of the Foot. Chronic irritation from tightly fitting shoes causes exostoses on the bones, and the formation of extraneous bursae. The common sites are the medial and upper aspects of the scaphoid, the dorsum of the first cuneiform, and the plantar and posterior surfaces of the calcaneus (calcaneal spurs).

Abnormal Curvature of the Spine. Abnormal curvatures of the spine are classified as: "scoliosis"—lateral curvature with the convexity to the right or left; "kyphosis"—anterior-posterior curvature with the concavity anteriorly; and "lordosis"—anterior-posterior curvature with the concavity posteriorly.

Scoliosis may result from postural influences, from congenital anomalies, from the softening of the bones in rickets and osteomalacia, from hemiparalysis of the spinal musculature, or from partial collapse of a hemithorax in chronic empyema. In many instances there is no evident cause. The vertebral bodies on the concave side are compressed, the spinal ligaments are thickened, and the ribs are pushed posteriorly to form the "razor back."

Two types of kyphosis are recognized: an adolescent type, seen in association with vertebral osteochondritis, vertebral epiphysitis, rickets, and tuberculosis, producing the characteristic "hunch back" (Hodgen and Frantz); and an adult variety, commonly known as "round back."

Lordosis is rare, and is usually secondary to deformities of the hips, muscular dystrophy, or shortening of the Achilles tendon.

Spondylolisthesis is an anterior displacement of the vertebral column on the sacrum in the fourth or fifth lumbar vertebra. It is caused by trauma acting on a congenital defect of the lamina of these vertebrae.

Deformities of the Thorax. "Flat chest"—shortness of the anterior-posterior diameter—often accompanies or is the cause of round shoulders. "Pigeon breast"—projection of the sternum anteriorly and caudally—is usually secondary to rickets or extreme dorsal kyphosis. Advanced grades of "funnel chest"—depression of the sternum—are usually congenital.

Congenital Defects of Osteogenesis

Osteogenesis Imperfecta. Three distinct forms of osteogenesis imperfecta are recognized: (1) *osteogenesis imperfecta congenita*; (2) *osteogenesis imperfecta tarda*; and (3) *idiopathic osteopsathyrosis*. The first two are congenital and are inherited as mendelian dominants. The bony lesions are associated with a blue coloration of the scleras of the eyes. In the third form there is no discoloration of the eyes. In the congenital type the disease is present at birth and there are multiple fractures as the result of birth trauma. In the tardy type the fractures are first observed when the infant starts to walk.

The bones of the extremities show the greatest degree of involvement. They are shorter, smaller, and thinner than normal. The cortex is thin and there is a decrease in the cancellous bone of the medulla. The bony lamellae are irregular. Microscopically a great excess of primitive osteoid is seen, without calcification and without organization into haversian canals (Riesenman and Yater).

The combination of blue sclera and osteogenesis imperfecta is known as Lobstein's syndrome, while if otosclerosis is also present (35 per cent) it is designated as van der Hoeve's syndrome.

Chondrodystrophy. Chondrodystrophy or achondroplasia is a disease characterized by defective formation of endochondral bone, so that all long bones are unusually short, and the victim is a dwarf with a normal-sized trunk, a normal-sized head, and short extremities. On the basis of the gross and microscopic appearance of the diaphyses three types are recognized: hypoplastic chondrodystrophy, in which

the zone of proliferate cartilage is inactive; malacic chondrodystrophy, in which the epiphyseal cartilage is softened; and hypertrophic chondrodystrophy, in which there is great hyperplasia of the zone of proliferate and hypertrophic cartilage, with retention of the orderly arrangement of cells. In the latter type, conversion of cartilage to bone proceeds

osteochondrodystrophia deformans (Morquio's disease) characterized by malacia and enlargement of the joints, hepatosplenomegaly, and mental retardation (Einhorn, Moore, Ostrum, and Rowntree). The endocrine type may be subdivided into hypophyseal dwarfism (infantilism or nanosomia), hypothyroidal dwarfism (cretinism), and gonadal dwarfism



Fig. 475. The skeleton in osteogenesis imperfecta.

in all directions, with minimal growth in the longitudinal direction (Opie and Allison).

Chondrodystrophy is inherited as a mendelian dominant. The condition can usually be recognized at birth and has no effect on the general health. The sunken appearance of the face is related to an inadequate growth of endochondral bone in the base of the skull.

General Considerations of Dwarfism. Dwarfism is a condition in which the body is abnormally undersized in comparison with the average of a particular species at a definite age. Two types are recognized: nonendocrine and endocrine. Of the former the more important are chondrodystrophy, renal dwarfism, and

(from precocious development and premature union of the epiphyses) (Werner).

Osteochondritis of the Growth Centers

In this category are collected a group of diseases involving various bones, each formerly designated by a distinctive name: Osgood-Schlatter disease of the tibial tubercle; Köhler's disease of the tarsal scaphoid and patella; Kienboeck's disease of the semilunar; and Legg-Calvé-Perthe disease of the proximal epiphysis of the femur (Gall and Bennett). The basic pathologic changes are rarefaction, necrosis, and fragmentation of the epiphysis. Causal factors are poorly understood.

Prolapse and Other Lesions of the Intervertebral Disks

In young persons, extrusion of the nucleus into the adjacent bone is a not uncommon finding. It represents a congenital anomaly or herniation because of a weak point in the cartilage plate, an apparently important causal factor in adolescent kyphosis. With increasing age there is a gradual loss in the elasticity of the disks, hyaline degeneration of the annulus, and loss of water from the tissues. All of these contribute to a decrease in the thickness of the disk.

The most important lesion of the disk from a clinical standpoint is posterior displacement or prolapse. Some degree of prolapse is found in about 15 per cent of all persons over thirty years of age. The most frequent site is the lower thoracic and lumbar region. In some cases the prolapse is extensive, presses on the cord or nerves, and requires surgical removal to relieve the symptoms (Donohue).

Osteopetrosis

In osteopetrosis, also known as "diffuse osteosclerosis" and "Albers-Schönberg disease," the bones are heavy, hard, thickened, difficult to cut, and inelastic. The cortex is increased in thickness, and the trabeculae are so numerous and large that little marrow is visible, and the line of junction of compacta and spongiosa is not distinct. About the metaphysis there are calcified islands of cartilage, surrounded by osteoid.

The inelasticity of the bones is responsible for the frequency of fractures. Replacement of the bone marrow causes the anemia, and may be extensive enough to result in extramedullary hemopoiesis in the liver and spleen. The deformities of the bones lead to the stocky build, square forehead, pigeon breast, bowed legs, atrophy of the optic nerves, arrested dentition, and frequent respiratory infections. If the condition is present at birth or develops in early infancy the prognosis is poor. Death is usually caused by intercurrent infection or by the anemia. The cause is unknown but a familial incidence has been observed (Clifton, Frank, and Freeman).

It is possible that the linear hyperostotic type of change termed "melorheostosis" is a similar condition (Franklin and Matheson).

Osteochondritis Dissecans

This is a noninfectious, aseptic necrosis of a segment of subchondral bone in one of the long bones, usually resulting in an osteocartilaginous sequestration into the joint. The overlying articular cartilage is normal. It is primarily a disease of men in the second decade of life, and the most frequent site is the



Fig. 476. An achondroplastic dwarf as represented in an early Egyptian statuette of Chnoum-hotep, who lived in the Vth Dynasty (about 2700 B.C.) and was "Chief of the Perfumes" or "Head of the Wardrobe" at court. (From an original photograph in Breasted: History of Egypt.)

medial condyle of the femur. The cause is unknown. The radiographic appearance is diagnostic.

Gargoylism

A disease, designated as gargoylism, lipochondrodystrophy, Hurler's disease, or dyostosis multiplex, and characterized by chondrodystrophic changes in the skeleton, corneal opacities, hepatosplenomegaly, and mental de-

iciency, occurs in children and is familial. The skeletal changes are essentially a decrease in velocity of endochondral ossification. The changes in the brain are in some instances identical with those of amaurotic family idiocy. In many tissues, there is an accumulation of fat in reticulo-endothelial cells and fibroblasts.

sexual organs, onset of menstruation, and rapid growth.

Incidence and Causal Factors. Fibrous dysplasia is slightly more common in girls than boys and has an onset usually before the twentieth year. It has been suggested that it is a variant of Hand-Schüller-Christian dis-



Fig. 477. Osteopetrosis of upper end of femur.

The latter two observations support the idea that gargoylism is a type of the lipid histiocytoses (Strauss).

Fibrous Dysplasia of Bone

Fibrous dysplasia is a disease entity, known also as Albright's syndrome, consisting of lesions of bone, pigmentation of the skin, and sexual and somatic precocity if in girls.

Pathologic Anatomy. The lesions of bone may be single or multiple, and if the latter tend to be on one side of the body. The single lesions fill the marrow cavity with firm white tissue containing few or many trabeculae of bone, and at times islands of hyaline cartilage. The white firm tissue is moderately collagenous connective tissue infiltrated with a few lymphocytes. With further growth, the cortex is eroded and the mass presents as an expanding tumor of bone (Lichtenstein and Jaffe).

The pigmentation occurs in about half of patients and is a deposition of melanin in the skin in small or large patches over the scalp, face, neck, back, and limbs. The sexual and somatic precocity is observed only in girls. It is manifested by development of the secondary

ease or a form of neurofibromatosis, but there are good reasons to question this (Albright).

Clinicopathologic Correlation. In a radiograph the lesions are expanding foci of rarefaction with a trabecular or stippled pattern. In the monostotic form the differentiation from tumors is not easily made and the polyostotic form resembles osteitis fibrosa cystica. Malignant tumors do not originate in fibrous dysplasia.

Paget's Disease

Pathologic Anatomy. In Paget's disease the pathologic changes are most advanced and most conspicuous in the skull, in the femur, and in the vertebral column. The bones are large and soft. On the surface there is a fine network of trabeculae instead of smooth, firm, cortical surface of a normal bone. The cortex is increased in thickness, largely by the addition of bone on the periosteal surface. In the skull and in the vertebrae the entire thickness of the bone is uniform in structure and is composed of an almost solid network of soft trabeculae, which can frequently be cut with a knife. In the femur and other long tubular

bones the marrow cavity is for the most part preserved and rarely decreased in size. The microscopic appearance is characteristic. There are irregular segments of lamellar bone, separated by short, irregular, and somewhat serrated cement lines. These cement lines stain

Monostotic Paget's Disease. So-called "monostotic" Paget's disease is seen in about 3 per cent of all autopsies. The lumbar vertebrae are most often affected. The pathologic changes are similar to those in the polyostotic type.

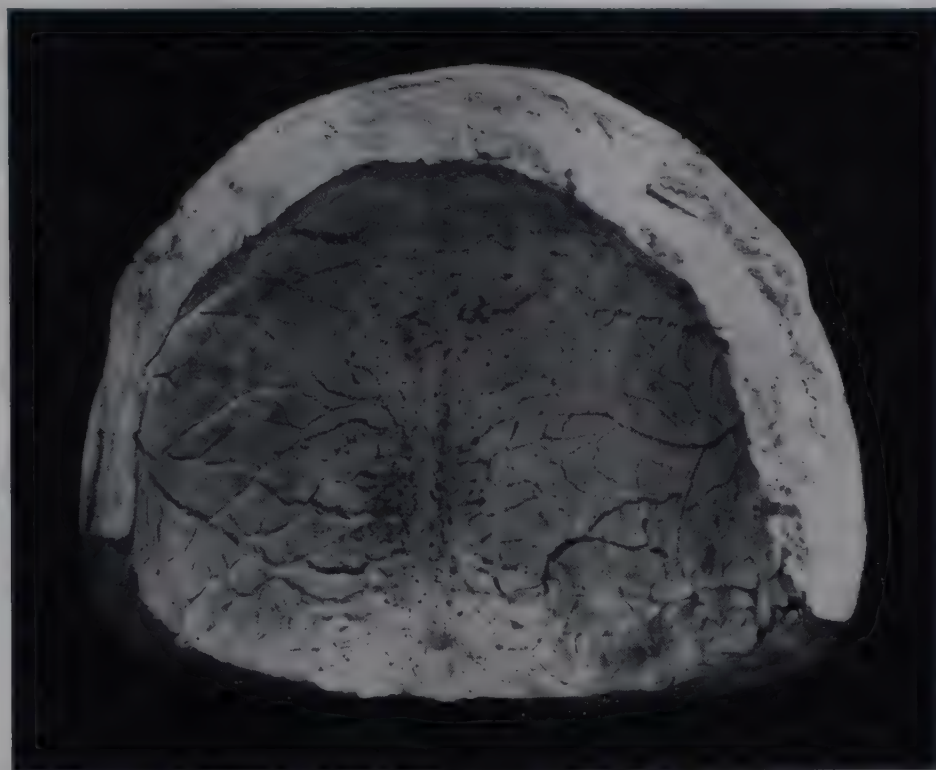


Fig. 478. Paget's disease of the skull.

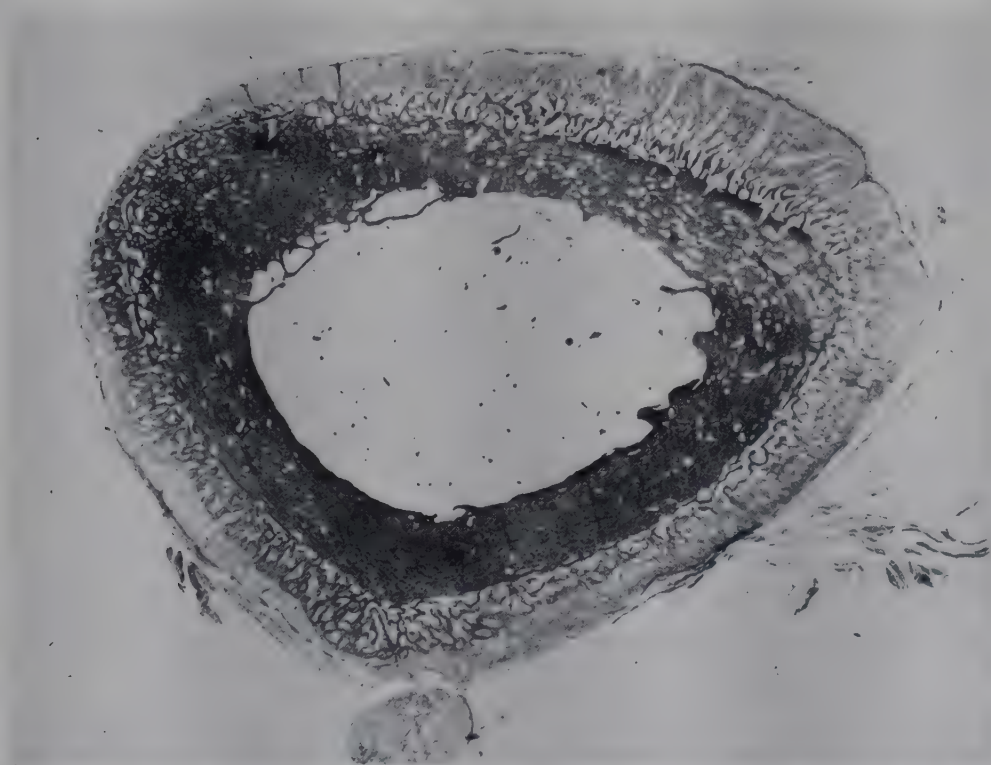


Fig. 479. Periosteal thickening of radius in pulmonary osteo-arthropathy. (Slide by courtesy of Dr. Granville Bennett.)

intensely with hematoxylin. The short fragments and segments are arranged in a mosaic pattern, with little tendency to form haversian canals. Within the marrow there are hemorrhage and fibrosis. About the body trabeculae there is a moderate number of osteoclasts and osteoblasts (Jaffe).

Incidence. Paget's disease is rarely seen before the age of forty years. It occurs in both sexes, in all races, and in all parts of the world. There is some evidence that it is familial.

Causal Factors. The high incidence of monostotic Paget's disease, especially in the vertebrae and other weight-bearing bones, suggests

that long-continued trauma is a causal factor. The occurrence of the condition at an age when osteoporosis is normally expected, taken together with the histologic picture, suggests that resorption of bone is the initial lesion, and that Paget's disease results from the attempt to repair the advancing loss of trabeculae. The parathyroid glands are uniformly normal.

Clinicopathologic Correlation. The disease runs a long, slow course, and is rarely the cause of death. The softness of the bones leads to lateral convexity of the femurs and bowlegs. The softness of the vertebrae and of the long tubular bones of the legs frequently leads to a decrease in height of from 2 to 3 inches. Softening of the neck of the femur results in coxa vara and the typical waddling gait of this deformity. Increase of the bone about the canal of the eighth nerve not infrequently leads to deafness. About 25 per cent of patients have some mental disturbance, probably related either to a decrease in the size of the cranial cavity or to the frequently associated arteriosclerosis of the cerebral blood vessels.

Osteogenic Sarcoma in Paget's Disease. About 25 per cent of all sarcomas of bone in persons over forty are apparently sequelae of Paget's disease. This factor further supports the hypothesis that sarcoma and carcinoma may result from extensive destruction and attempted repair of tissues.

Clubbing of the Fingers and Hypertrophic Pulmonary Osteo-arthropathy

Clubbing of the fingers is a painless, uniform enlargement, confined to the distal segment. There is hyperplasia of the fibro-elastic tissue of the nail bed and of the fatty connective tissue of the ball of the finger. There are dilatation of vascular spaces, new formation of capillaries, and thickening of the capillary walls.

In hypertrophic pulmonary osteo-arthropathy there is focal and diffuse new formation of bone in the periosteum of the bones of the forearm and hand. The original cortex becomes porotic. It is probably only an extension of the same basic process responsible for clubbing.

Clubbing of the fingers may be hereditary, but most examples are associated with disease of the heart, lungs, mediastinum, or vascular supply of the extremities. The essential physi-

ologic change and probable cause are an increase of blood flow per unit of tissue and an increase of arterial pressure in the digital vessels (Mendlowitz).

Osteoporosis

Osteoporosis is a rarefaction in bone seen in association with increasing age, in hyperparathyroidism, in hyperthyroidism, in basophilism, in bones which are not used, and in osteomalacia. The cortical bone is much thinner than normal, and the sparse thin trabeculae are smooth. In the vertebrae the elastic disks expand and the bodies take on a biconcave shape. Small herniations of cartilage into the bone are common and are known as "Schmorl's nodules." In the senile type there is no change in the serum calcium and phosphorus. The cause is unknown but dietary deficiency and disturbances in absorption of calcium because of achlorhydria are prominent factors (Black, Ghormley, and Camp).

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CXIV

Tumors Peculiar to Bone

The tumors which originate in bone are related to the cellular types present: bone, cartilage, fibrous tissue, fat tissue, blood vessels, and the various cells of the marrow.

The comparative frequency of involvement of the various bones is well shown in Table 59 (Christensen). This tabulation brings out that tumors of bone are far more common in the long tubular bones of the lower extremities

moderately severe trauma to the exposed bones of the extremities. It is also possible that the early sarcoma of bone is responsible for the injury, in that the extremity, because of the sarcoma, is not as adept in avoiding a collision as would be a normal extremity. In summary, the relation of trauma to sarcoma of the bone must be regarded as unproved but possible.

TABLE 59. INCIDENCE OF TUMORS OF BONE

Bone	Osteoma and Exostoses	Osteogenic Sarcoma	Giant Cell Tumors	Multiple Myeloma	Endothelial Myeloma	Others
Skull.....	1	8	2	2	3	2
Maxilla and mandible..	3	15	41	2	3	0
Vertebrae.....	1	8	27	8	4	7
Humerus.....	2	54	29	1	10	8
Radius and ulna.....	1	15	48	0	3	1
Femur.....	12	174	100	7	16	11
Tibia and fibula.....	7	104	79	5	18	2
All others.....	8	63	36	3	27	16

than in any other bone, and that the region of the knee is the most frequent site. It seems logical that this observation may have some bearing on the cause of the tumors. Sarcoma of bone is found most frequently in the younger age groups, and both osteogenic sarcoma and endothelial myeloma are more common in the male sex.

Causal Factors. Relation to Trauma. Little is known about the cause of bone tumors. Throughout the literature there is repeated emphasis on the possible relation of trauma to the onset of a tumor. In from 20 to 40 per cent of patients with a sarcoma of bone there is a history of recent significant trauma. However, in evaluating this factor it is necessary to remember that most persons in the second and third decades of life frequently suffer some

Clinicopathologic Correlation. Tumors of bone are similar to other tumors in that the principal signs and symptoms result from the presence of a mass of new tissue. This may take the form of a fusiform or nodular swelling along the course of a bone. As the tumor increases in size, there is impingement on the surrounding nerves, blood vessels, and muscles, and occasionally gangrene results from occlusion of the blood vessels. The expansion of the tumor within the substance of the bone, and pressure on the periosteum and the surrounding nerves, are responsible for the pain that is so frequent in tumors of bone. Sarcomas in general are rich in blood supply, and hence some tumors may exhibit an expansile pulsation, similar to that observed in aneurysms.

Exostoses. Osteochondroma. Osteoma

Pathologic Anatomy. The exostosis or osteochondroma is a small, lobulated elevation on the periosteal surface near the ends of the long bones at the sites of insertion of the tendons. The protuberance consists of definite layers. The tendinous fibers insert into a delicate connective tissue that forms a thin capsule over the next deeper layer of hyaline cartilage. Finally there is a central and deepest layer of

Osteoma. On the external surface of the frontal and parietal bones hemispherical or irregular bony masses, termed osteomas, are observed, composed of spongy trabecular or dense compact bone. It is not certain that they are true neoplasms.

Osteoid Osteoma

A distinctive focal lesion of bone known by many names, e.g., sclerosing nonsuppurative osteomyelitis and sclerosing osteomyelitis of

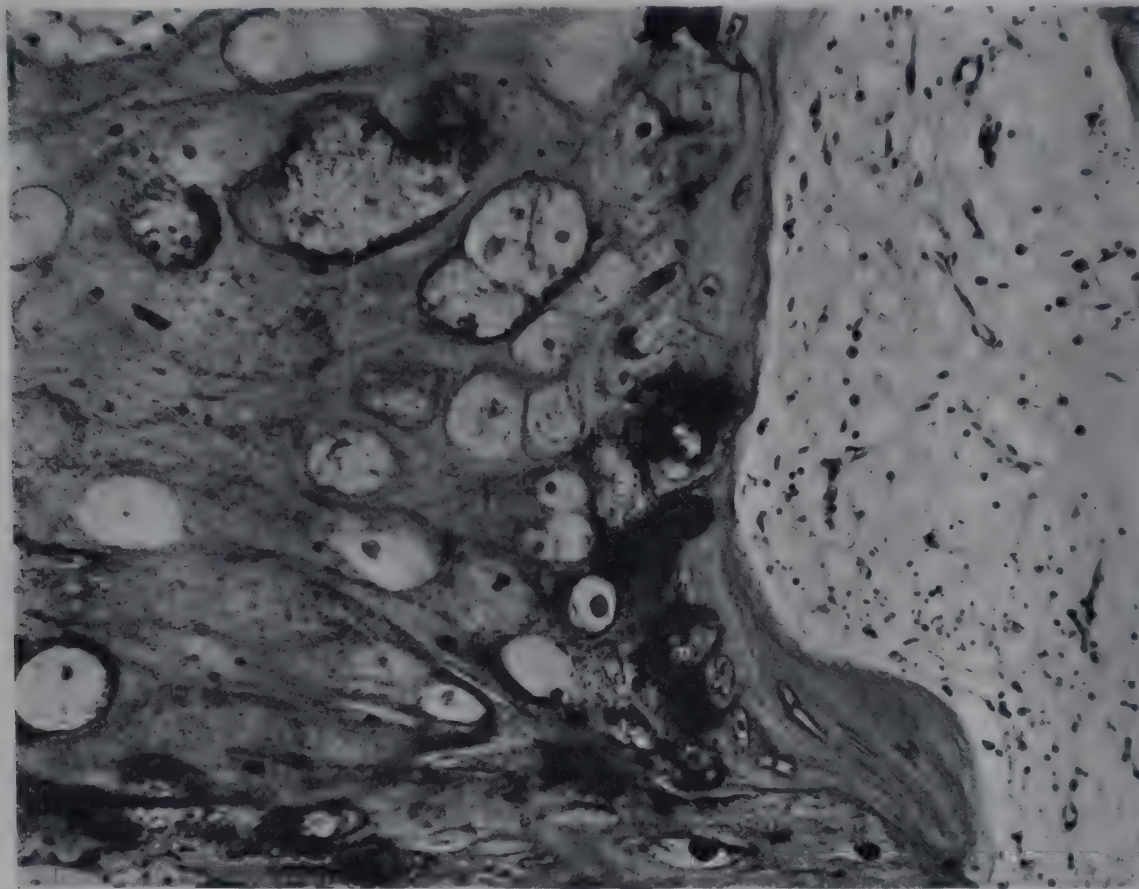


Fig. 480. Base of an exostosis in multiple cartilaginous exostoses.

cancellous bone. Microscopically the cartilage and bone are seen to be characteristic, with endochondral ossification proceeding normally at the junction of the two. The bone of the exostosis merges with the trabeculae of the underlying cortex without transition.

Exostoses are more common in younger persons, and rarely produce symptoms. They are probably derived from remnants of primitive cartilage in the periosteum. Occasionally a malignant chondrosarcoma or osteogenic sarcoma appears to arise in an exostosis.

Multiple Cartilaginous Exostoses. In this condition, also known as "hereditary deforming chondrodystrophy," there are many exostoses together with deformities and anomalies of the bones. The exostoses may reach large size and impinge on nerves, blood vessels, and other structures. The condition is hereditary. (Fig. 480.)

Garré, was first accurately defined by Jaffe in 1935.

Typically the lesion is a spherical red mass of tissue, 0.5 to 1 cm. in diameter in a long bone, sharply demarcated from the surrounding bone. In radiographs there is a central nidus of rarefaction surrounded by dense bone, which in turn in some instances is enclosed in a narrow zone of rarefaction. The nidus is composed of cellular immature osteoid tissue. The sclerotic layer is dense bone (Jaffe and Lichtenstein).

Almost all examples are solitary, and the tibia, neck of the femur, os calcis, phalanges, and navicular bones are most frequently involved. The tumor grows slowly.

Chondroma

The chondroma of bone is typically a lobulated, firm tumor, most frequently found in

the hands and feet, in the ribs, and in the vertebral column. The bluish gray matrix is divided into lobules by narrow connective tissue trabeculae. Small foci of calcification and cyst formation are common. In the tubular bones the cortex is intact and forms a thin capsule over the tumor. The typical appearance of hyaline cartilage is observed. The cells, in pairs or tetrads, are arranged irregularly in a palely basophilic matrix. In some areas there is myxomatous degeneration of the matrix, or actual neoplastic proliferation of myxoblasts—hence the term “chondromyxoma.” Malignant transformation to a chondrosarcoma occurs, especially in the long bones and in the sternum.

Chondroma is observed most frequently in the third decade, and grows slowly. Recurrence is not uncommon. No causal factors have been established.

Chondromyxosarcoma

Chondromyxosarcomas are lobulated, firm or soft tumors, growing on the surface of the cortical bone, and rarely perforating into the marrow cavity. On section there is a soft, bluish gray, granular or homogeneous tissue, with numerous foci of cyst formation and hemorrhage.

The characteristic cell is spindle-shaped or stellate, and is arranged in a syncytium, separated by a hyaline matrix. Scattered round cells in the matrix have a chromatic nucleus and clear cytoplasm. Mitoses are abundant. Foci of ossification may rarely form, either in the primary tumor or in metastases.

Some investigators believe that the chondromyxosarcomas are of two types: primary, arising directly from apparently normal bone; and secondary, a malignant transformation of a preexisting benign tumor. This opinion is supported by differences in distribution, age incidence, prognosis, and microscopic appearance (Geschickter and Copeland).

Chondromyxosarcoma is twice as common in men as in women, and may be seen at any age from fifteen to fifty. Five-year cures do not exceed 20 per cent.

Giant Cell Tumor

The giant cell tumor of bone is characteristically a solitary tumor in the epiphysis or

epiphyseal end of a tubular bone. A special type known as an “epulis” is seen in the jaw.

Pathologic Anatomy. The end of the bone is expanded, and a thin bony shell forms the outline of the tumor. The neoplastic tissue is dark reddish brown, soft, and friable. Secondary changes such as hemorrhage, necrosis, and cyst formation are common in the larger tumors. The overlying articular cartilage may be deformed or perforated. The preponderant cell is a spindle-shaped or ovoid cell similar to that of primitive connective tissue. The nuclei are relatively large, and have prominent central nucleoli. Between the cells there is a variable amount of collagen. Irregularly distributed throughout this stromal background are numerous giant cells. The number of nuclei varies directly with the size of the cell. The abundant cytoplasm is granular or vacuolated. The blood vessels are thin-walled and are lined with flattened cells.

Variants of the Giant Cell Tumor. Spindle cell variants, chondromatous variants, xanthomatous variants, and myxomatous variants of the giant cell tumor have been described in the literature. It is probable, however, that these are distinct tumors rather than variants of the giant cell tumor (Jaffe, Lichtenstein, and Portis).

Epulis. The term “epulis” is used to designate all solitary, tumorlike lesions developing from the periosteum of the maxilla or mandible and appearing clinically as circumscribed swellings beneath the gums. Some are true giant cell tumors, while others are fibromas and reparative hyperplasias. They are covered with stratified squamous epithelium, showing acanthosis and hyperkeratosis. A sequential relation to the extraction of a tooth is frequently recorded.

Giant Cell Xanthomatous Tumors of Tendons. These yellow firm neoplasms are seen most frequently on the flexor tendons of the fingers. The stroma is similar to that of the giant cell tumor, with giant cells and foam cells (Mason and Woolston).

Malignant Giant Cell Tumor. An occasional giant cell tumor exhibits invasive tendencies and may even metastasize. In addition to the characteristic giant cell of the benign tumor, there is in these malignant types a true tumor giant cell (Stewart, Coley, and Farrow).

Histogenesis and Causal Factors. A history of significant trauma is occasionally secured,

and this, with the histologic picture, has suggested that the giant cell tumor is essentially a reparative process (Mallory). Geschickter and Copeland consider it a hyperplasia of osteoclasts in a region where intracartilaginous bone was formed.

Reticulum Cell Sarcoma

The reticulum cell sarcoma is a tumor of late middle life in the ends of the long tubular bones. The marrow cavity is filled with a gray, firm, and fleshy tissue, and the cortical bone

found in other bones, especially those of the skull.

Angio-endothelioma. Under this term or related ones a number of solitary and multiple tumors of bone have been described (Ewing). Even those who accept endothelioma of bone as an entity find that the possibility of a metastatic tumor must be eliminated.

Liposarcoma

This is an exceedingly rare tumor of bone, of which there are fewer than ten case reports

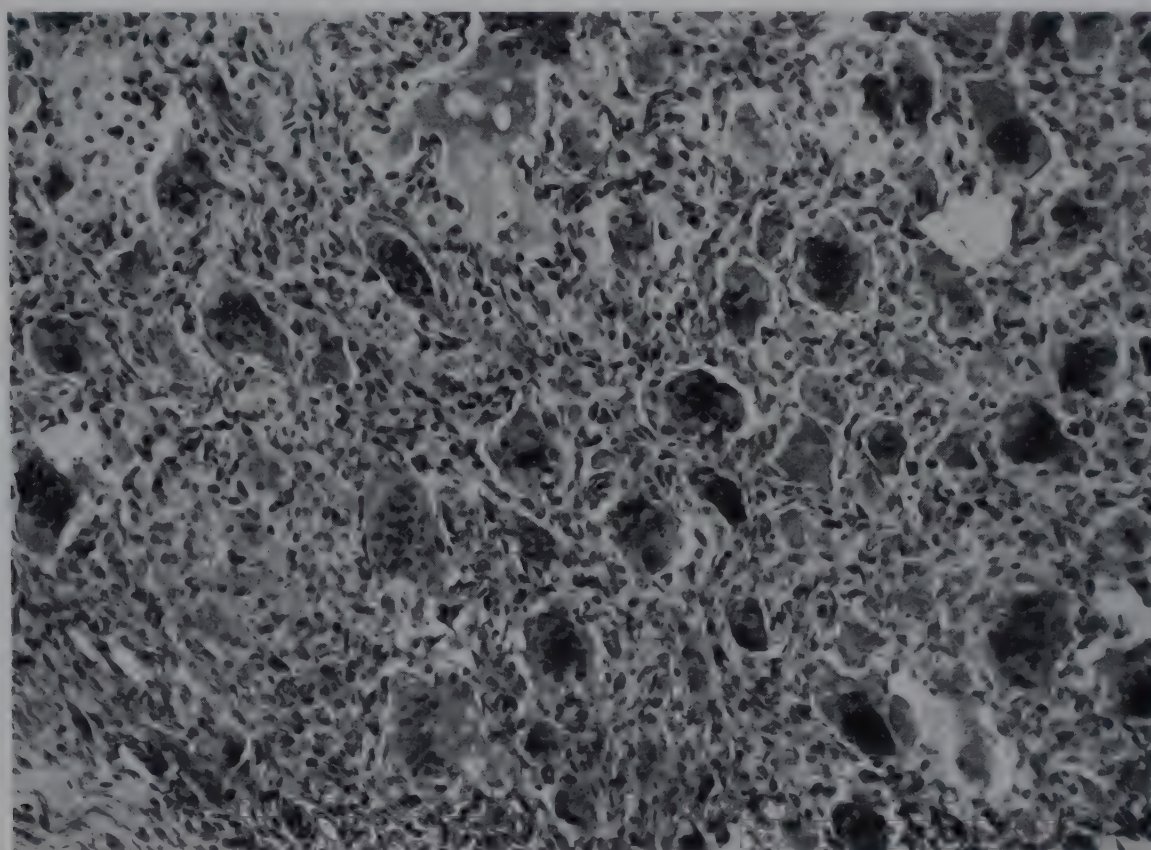


Fig. 481. Giant cell tumor of bone. (Armed Forces Institute of Pathology, Neg. No. 63503.)

is eroded. The type cell is identical with that of the reticulum cell sarcoma of other tissues. A delicate reticulum may be demonstrated around groups of cells and between individual cells. Invasion of veins is the rule.

The prognosis is relatively good if treated by early amputation. Trauma is apparently not an important causal factor (Parker and Jackson).

Angioma. Angio-endothelioma

Angioma. About 10 per cent of all persons have in one or more vertebrae small cavernous hemangiomas (Makrycostas). Occasionally they reach sufficient size to cause collapse of the vertebra or pressure on the cord (Bucy and Capp). Similar tumors are occasionally

found in the literature. The tumor is multiple, or shows an early tendency to metastasize to other bones. The cells are polymorphous and contain small vacuoles of fat (Rehbock and Hauser).

Osteogenic Sarcoma

The term "osteogenic sarcoma" comprehends a number of distinct neoplastic types that all originate in bone and in the surrounding attached tissues. Six types are recognized: (1) medullary and subperiosteal, (2) telangiectatic, (3) sclerosing, (4) periosteal, (5) fibrosarcoma, medullary or periosteal, and (6) parosteal and capsular (Ewing).

Medullary and Subperiosteal Osteogenic Sarcoma. These tumors apparently arise be-

neath the periosteum and infiltrate and replace the marrow cavity and elevate the periosteum. The shaft of the bone is destroyed, and the periosteum is eventually perforated so that the tumor grows out into the surrounding soft tissue. Grossly the neoplastic tissue appears grayish white, but hemorrhage and necrosis are so common and extensive that only a friable dark red tissue may be evident. Small bluish gray foci of cartilage are occasionally seen. Extreme pleomorphism of the cells is

ing mass forms. There are large sinusoidal spaces, lined and separated from one another by neoplastic cells similar to those of the medullary and periosteal osteogenic sarcoma. The prognosis is poor.

Sclerosing Osteogenic Sarcoma. Typical sclerosing osteogenic sarcoma is a grayish white, firm tumor between the cortex and periosteum on the shaft side of the epiphyseal line of the long tubular bones in a person less than thirty years of age. On section the tumor

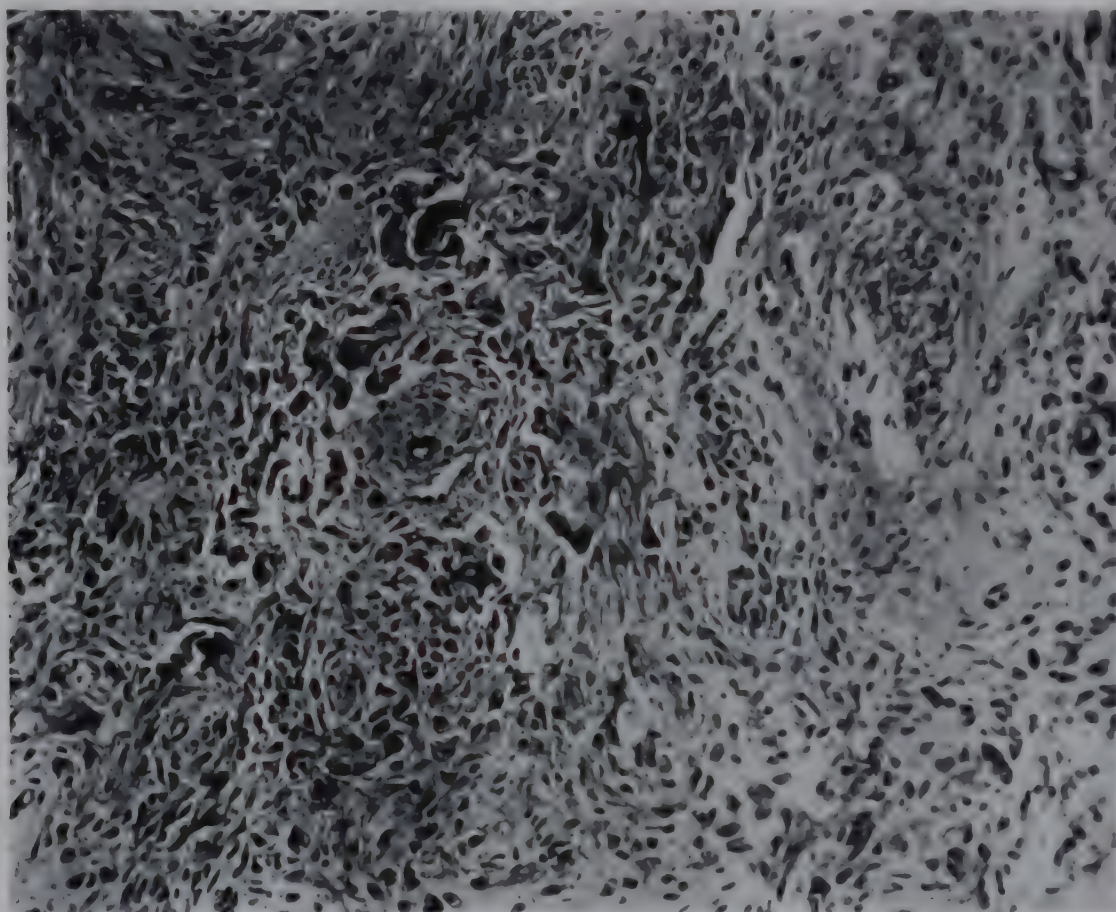


Fig. 482. Osteogenic sarcoma.

observed microscopically. All sizes and shapes are easily recognized, and tumor giant cells are abundant. Between the cells in some regions there is an immature, atypical osteoid or cartilage (Fig. 482). Rarely definite bony trabeculae are formed. Vascular spaces are lined by tumor cells.

This type of osteogenic sarcoma is most frequently situated in the lower end of the femur, in the upper end of the tibia, and in the upper end of the humerus, and is rarely seen after the age of twenty years.

Telangiectatic Osteogenic Sarcoma. This is a rapidly growing tumor of bone in children and young adults, starting in the ends of the shafts of the long tubular bones. The bone is destroyed early and replaced by a vascular, soft, red tissue. The surrounding muscle is invaded and a large fusiform or globular pulsat-

ing mass forms. There are large sinusoidal spaces, lined and separated from one another by neoplastic cells similar to those of the medullary and periosteal osteogenic sarcoma. The prognosis is poor. There are all stages from primitive spindle cells through osteoid to well formed, dense, bone. Osteoblasts with large vesicular nuclei are conspicuous, and multinucleated forms are seen. Five-year cures follow amputation in 20 to 30 per cent of cases.

Periosteal Sarcoma. This rare neoplasm forms a tumor on or encircling the shaft of the long bones. It is firm, and foci of necrosis and hemorrhage are rarely seen. Microscopic examination reveals closely packed, small spindle cells, without intercellular substance. Metastases occur early, and are widespread.

Fibrosarcoma. Fibrosarcoma of the bone

may arise on the periosteal or endosteal surface. It is a firm, frequently encapsulated tumor of grayish white whorled tissue, with abundant intercellular collagen. The femur and the tibia are the most common sites, and the majority of the patients are between twenty-five and forty. In general the tumors

especially the vertebrae, ribs, sternum, skull, and femur. Rarely there is diffuse replacement of the marrow, rather than discrete tumors. Trabecular and cortical bone is locally resorbed giving punched-out foci of radiolucence in the radiograph. Spontaneous fracture may occur. The other organs are essentially normal

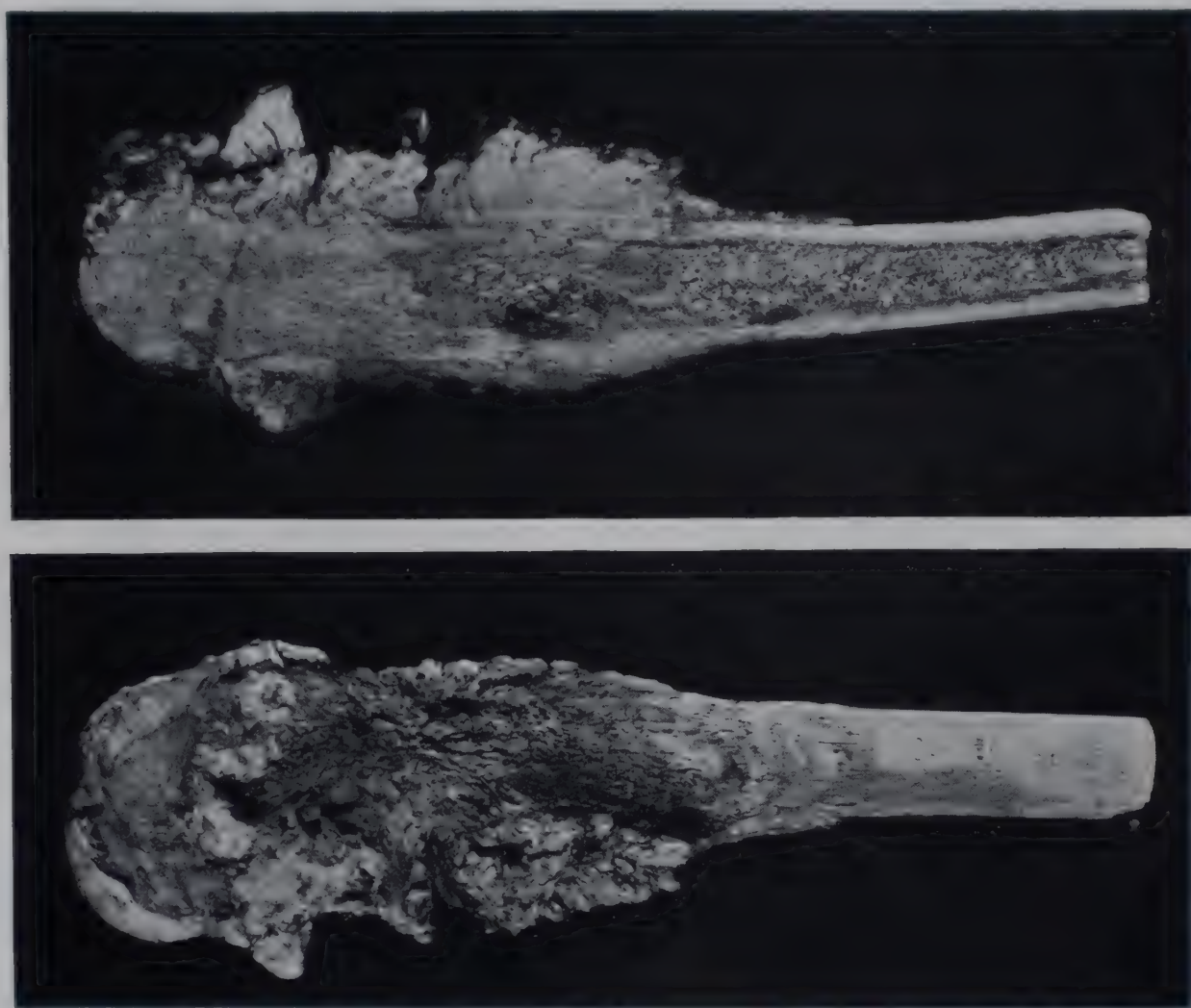


Fig. 483. Osteogenic sarcoma of femur.

are relatively benign, and prognosis is good if treatment is prompt.

Parosteal and Capsular Sarcoma. In this category are placed the sarcomas originating in the soft tissues about the joints and bones. On the basis of microscopic examination they are divided into fibrosarcomas, liposarcomas, and completely undifferentiated sarcomas. The joint cavity and bone are rarely invaded. Clinically those originating in the capsule of the knee joint and of the ankle are characteristic.

Multiple Myeloma

The myeloma is a tumor of bone, characteristically multiple, affecting persons over forty years of age, and derived from the specific cells of the bone marrow.

Pathologic Anatomy. There are multiple, circumscribed but not encapsulated, grayish red, spherical or ovoid tumors in the bones,

except the kidneys, which may be decreased in size and firm, with an irregularly granular surface.

Although myeloid, erythroid, and lymphoid types of myeloma have been described, it is probable that all myelomas are of the plasma cell type. The typical cell has an eccentrically placed nucleus in an amphophilic cytoplasm (Fig. 484). Chromatin is broken into small masses and arranged about the nuclear wall. There is a perinuclear halo. There may be vacuolation of the cytoplasm and binucleated cells occur. In the kidney there are hyaline casts associated with a variable degree of fibrosis and cellular infiltration (Bell).

Solitary Myeloma. Inasmuch as most examples of solitary myeloma of bone progress to the multiple stage there seems to be little advantage in separating it as a distinct type (Bayrd and Heck).

Extramedullary Plasmacytoma. This histologically identical tumor is observed most frequently in the oropharynx (Hellwig). Association with myeloma of bone is observed.

cell derived from reticulo-endothelial cells, but no exact knowledge is available.

Effect of Treatment. Stilbamidine (4,4'-diamidinostilbene) in some patients gives re-

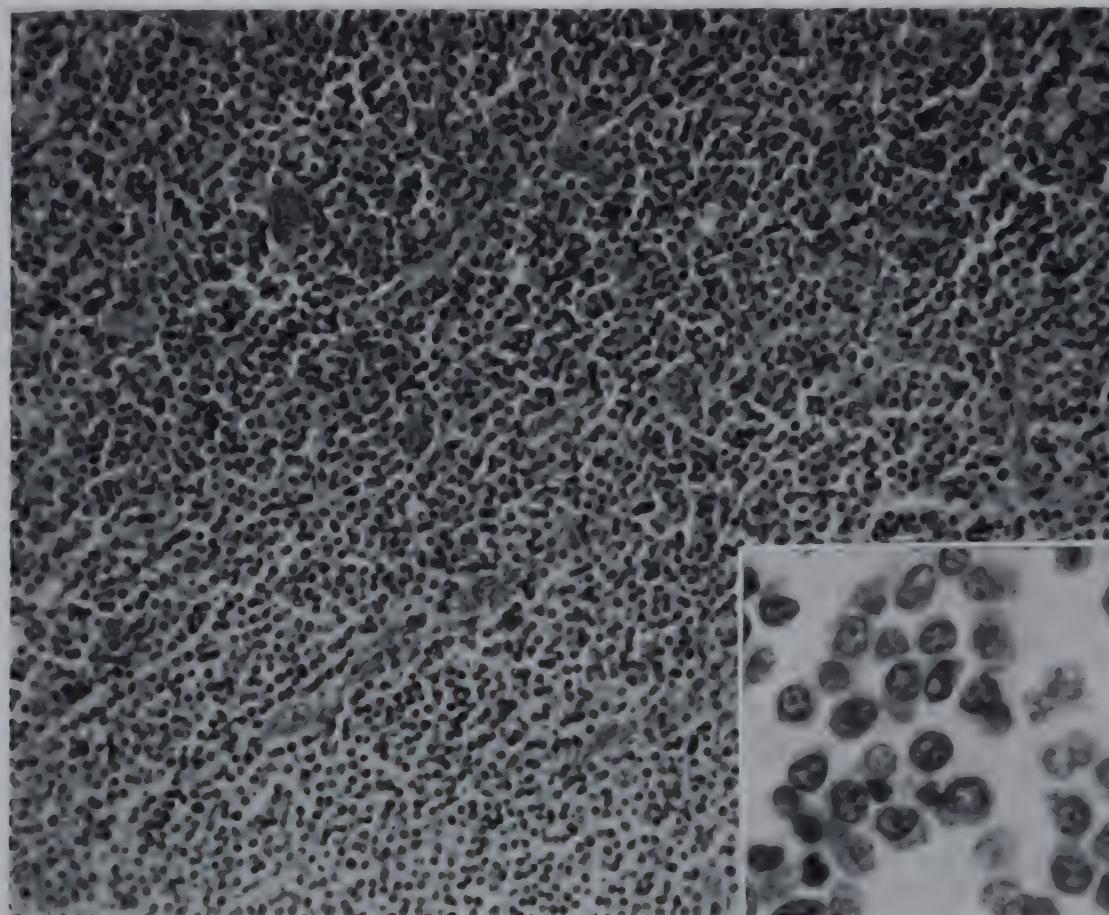


Fig. 484. Multiple myeloma of bone.

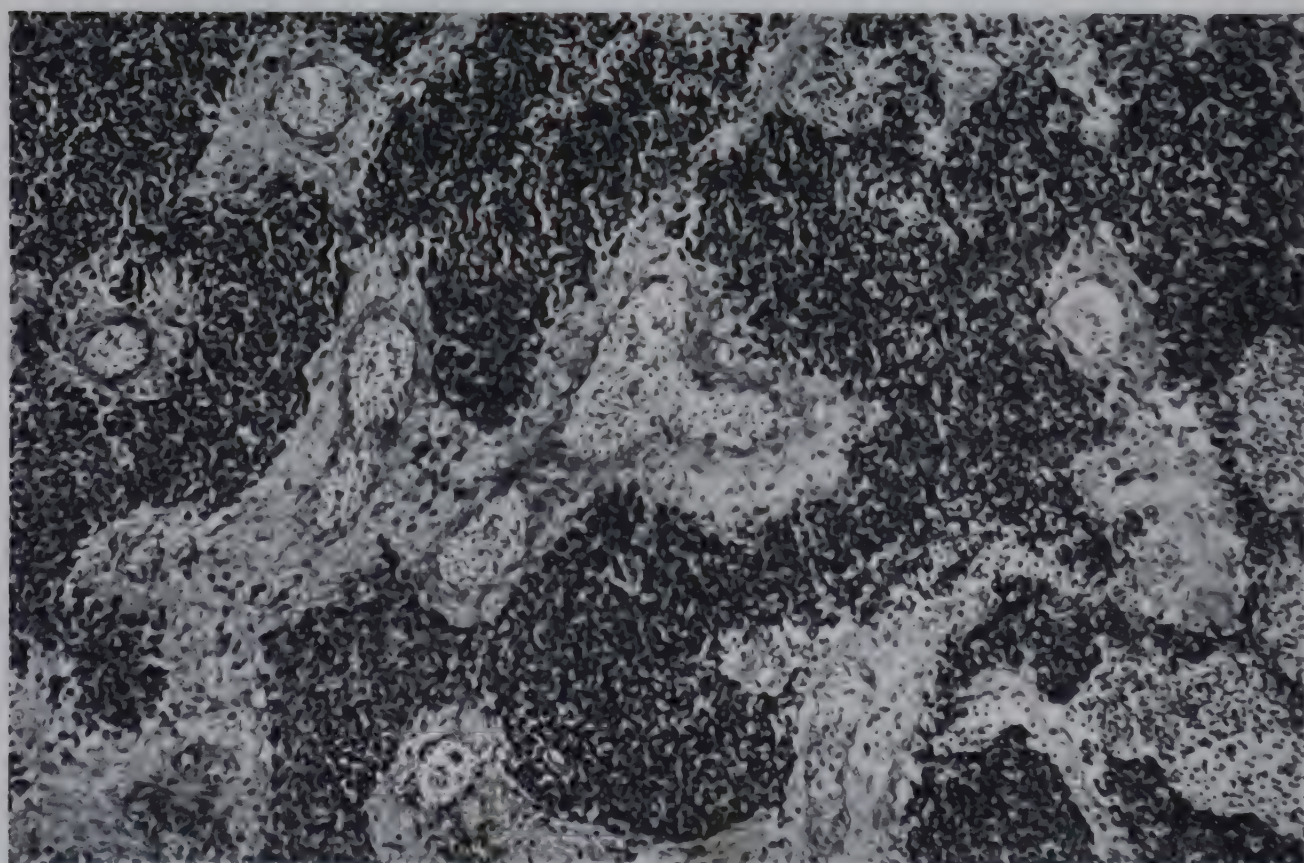


Fig. 485. Ewing's sarcoma of bone. (Armed Forces Institute of Pathology, Neg. No. 73775.)

Incidence. Myeloma is a disease of men, in a ratio of 3 to 1, over forty years of age.

Histogenesis. It has been suggested that the myeloma cell is a dysplastic type of plasma

cell derived from reticulo-endothelial cells, but no exact knowledge is available. After treatment cytoplasmic masses of ribose nucleic acid appear (Snapper).

Clinicopathologic Correlation. The pain is probably related to small trabecular fractures. Compression collapse of a vertebra leads to cord or root signs. Hyperproteinemia up to 23 gm. and hyperglobulinemia up to 15 gm. occur in three-fourths of patients. In about half, there is elevation of serum calcium, phosphorus, and phosphatase (Gutman, Tyson, and Gutman). These alterations in the serum are apparently unrelated to the presence or absence of Bence Jones proteinuria which is observed in half of the patients (see p. 16). Renal failure results from blockage of the tubules by casts and fibrosis. Myeloma cells may appear in the peripheral blood and at times there is no sharp distinction between myeloma and plasma cell leukemia.

Ewing's Sarcoma

Pathologic Anatomy. The typical example of Ewing's sarcoma, also known as "diffuse endothelioma" and "endothelial myeloma," is a fusiform swelling of one of the long tubular bones. The fusiform mass is firm and is composed of a homogeneous, finely granular, yellowish gray tissue, moderately well circumscribed from the surrounding muscles and fascias. The cortical bone in the area of swelling is thickened and increased in density. The individual tumor cells are polyhedral or round, and are arranged in groups, separated from one another by bands of connective tissue. The nuclei of the cells are relatively large and moderately chromatic. The cytoplasm is scanty and acidophilic. Within the masses of tumor cells there are small vascular spaces, lined by the tumor cells (Fig. 485). The edge of the tumor, where it is in contact with muscle, shows moderate infiltration, and in the narrow cavity tumor cells may extend for some distance upward or downward beyond the grossly visible tumor on the outside of the bone. There are late metastases, most frequently to the lungs and to other bones, notably the scapula, clavicle, and vertebral column. It is possible that these nodules in other bones represent multiple primary tumors rather than metastases (Lichtenstein and Jaffe).

Histogenesis. The intimate relation of vascular spaces to tumor cells led Ewing to postulate that this tumor originates from capillary endothelium. Perivascular mesenchyme and lymphatic endothelium have also been sug-

gested as sites of origin. Reports in the literature have stated that at least some of the examples of Ewing's sarcoma of bone are actually metastases from a neuroblastoma of the adrenal or other nervous structure (Willis). Further work is necessary to establish this concept.

Incidence and Causal Factors. Over 95 per cent of patients with Ewing's sarcoma are under thirty years of age, and the sex preponderance is about 2 to 1 in boys. The long tubular bones are most frequently involved. The flat bones are occasionally the seat of a primary tumor. In about one-half of instances there is a definite history of trauma.

Clinicopathologic Correlation. The characteristic intermittent attacks of pain, fever, and leukocytosis are probably related to hemorrhage into the tumor. The tumor cells are remarkably radiosensitive, but the prognosis is poor. The lack of destruction of bone until late accounts for the rarity of spontaneous fracture (Hamilton).

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CXV

Diseases Peculiar to the Teeth

The teeth are formed of two basic components: an ectodermal component that develops into the enamel organ and enamel, and a mesoblastic component that contributes the dentin, cementum, periodontal membrane, and pulp. They differ from most tissues in that there is no continued growth after eruption, there is no replacement of destroyed elements, and each person is bequeathed two complete sets: the deciduous dentition and the permanent dentition.

The examination of the teeth may yield important information about a patient's health. The teeth and gums are not infrequently involved in systemic disease—leukemia for example. The tissues of the gums are susceptible to the action of hormones, particularly the estrogens, and their condition may give a clue to an increase or decrease of these hormones in the body fluid. Of great interest is the hyperplasia of the gums in those taking dilantin sodium. The deposit of enamel and dentin is affected by many nutritional and growth factors, so that some facts of the past history may be read in the teeth. The enamel organ is an ectodermal structure and may be involved in anomalies affecting the ectoderm (Anderson).

Congenital Anomalies of the Teeth

All or some of the teeth may fail to form—total or partial anodontia. The basic defect is a failure of the formation of the enamel organ. The anomaly is not infrequently associated with other disturbances of ectodermal structures. Partial anodontia is in many instances a part of hereditary ectodermal dysplasia, with absence or hypoplasia of the sweat glands (the anhydrotic type), hair, and nails. The primitive dental band may give rise to additional enamel organs to form predeciduous teeth, post-permanent teeth or a third dentition

(never complete), and supernumerary or accessory teeth, depending on the position and rate of development of the additional enamel organ. Impeded eruption of the third molars or “wisdom teeth” is common because of the misdirection of the axis, and they are frequently the site of infection. Aplasia or hypoplasia of the enamel and of the dentin (dentinogenesis imperfecta) is inherited as a dominant character.

Hypoplasia of the Enamel

The enamel prisms are deposited by the enamel organ in a definite pattern and in a definite chronology to form the crown of the tooth. If at a certain time there is some local or systemic disturbance that interferes with the deposition of enamel, the tooth will show a pit or depressed ring at the point which corresponds to the time when the disturbance occurred. In the deciduous teeth most of the enamel is deposited before birth, and hypoplastic defects are related to events during intra-uterine life. Most of the enamel of the permanent teeth is deposited after birth, and defects are related to rickets, tetany, exanthematic diseases, and other infectious diseases of childhood (Sarnat and Schour).

Periodontitis

Pathologic Anatomy. The essential pathologic change in periodontitis, also known as “pyorrhea alveolaris” or “Riggs’ disease,” is an inflammation of the marginal gingivae. There are edema, hyperemia, and infiltration with lymphocytes and plasma cells. The periodontal membrane separates from the cementum, and a pocket forms between the tooth and the gingiva. This becomes filled with food and calculus, and squamous epithelium grows

down to cover the retracted gum. This inflammation becomes purulent, and pus exudes from the pocket. At times small abscesses form that drain into the pocket or through a sinus tract in the gingivae. Early there is resorption of the alveolar bone, and the space thus created is filled with granulation tissue. The teeth are no longer held by the bone and are loose in their sockets.

Causal Factors. True periodontitis is essentially a local disease. The causes are mechanical irritation from deposits of calculus, poorly fitting crowns, bands, and fillings, impaction of food in crevices created by malocclusion of teeth, and oral sepsis. An inadequate diet, an endocrine dystrophy, or systemic disease may serve as predisposing factors.

Periodontosis. In some persons with separation of the gingivae from the neck of the tooth and growth of the epithelium over the pocket, the alveolar bone is resorbed and the tooth becomes loose, but there is no primary inflammation. The condition appears to be a local expression of some disturbance of metabolism bringing about resorption of bone.

Gingival Recession. In contrast with periodontitis, in which a pocket is formed, gingival recession is a retraction of the gingivae on the neck of the teeth without the formation of pockets. The exposed cementum is calcified. The epithelium of the gingivae is thickened and keratinized, and the connective tissue is preserved. It is apparently related to faulty brushing of the teeth.

Other Types of Gingival and Alveolar Atrophy. Normally with increased age there is atrophy of the alveolar crest and gingivae, exposing the cervices of the teeth. A similar change occurs from nonuse of the jaws, from lack of an opposing surface for one or more teeth following extraction, and in malocclusion. Examination of the jaw and teeth may give important information in the identification of bodies.

Dental Caries

Dental caries is one of the major problems of dentistry. It involves destruction of enamel, thus impairing the masticatory function of the teeth, and, more importantly, opening the dentin and the pulp to bacterial infection.

Pathologic Anatomy. Caries most frequently begins on the proximal smooth sur-

face of the tooth, just below the contact point, and is a focus of decalcification of enamel. Bacterial invasion follows, and the decalcified mass drops out to form a cavity. Histologic examination shows three layers about the cavity. On the surface is a zone of amorphous debris, fragments of food, and masses of bacteria. Next is a midzone of decalcification in which the outline of the prisms is discernible as a granular mass. Finally there is a zone of partial decalcification. The enamel prisms are distinct, but the cement substance is disintegrated.

As the cavity advances through the enamel there are secondary changes in the dentin. The odontoblastic processes in the dentinal tubules show fatty degeneration. The dentin about the foci of caries is more highly calcified than normal dentin, and that immediately exposed to the carious cavity is opaque and granular. Bacteria invade along the dentinal canals, enlarged by resorption, and are easily identifiable in section. Secondary dentin is formed on the pulpal surface and is characterized by fewer dentinal canals than normal.

In acute cases the dissolution of the calcium in the enamel and dentin proceeds more rapidly, and there may be a little surrounding reaction. If the cavity starts on the root, the first changes are in the cementum rather than in the enamel. After the pulp of the tooth has been opened the carious process may proceed outward and attack the dentin first—central caries.

Incidence. Dental caries affects both the deciduous and the permanent teeth. The incidence increases progressively to the third or fourth decade, when the process frequently becomes quiescent, only to be reactivated in the sixth decade. One study of 10,445 college students showed slightly over ten carious teeth per person. Caries is somewhat less common in primitive peoples.

Causal Factors. The cause of dental caries is not definitely known. There is evidence for many factors—carbohydrate content of the diet, type of bacterial flora in the mouth, fluorine content of water, and others.

Pulpitis

Inflammations of the pulp may be acute or chronic. Bacteria usually enter through a carious cavity, but a blood-borne infection may occur. The gross and microscopic features

are essentially those of acute and chronic inflammations in other tissues, together with formation of secondary dentin, and calcification or ossification of a part of the pulp (pulp stones).

matory edema of the pulp and consequent increased pressure within the limited space may bring about occlusion of the vessels and necrosis of the pulp (Robinson and Boling).



Fig. 486. *A*, Infiltration and ulceration of the gingivae in monocytic leukemia. *B*, Hypertrophy of the gingivae associated with hormonal dystrophy at puberty. *C*, Odontogenesis imperfecta (hereditary opalescent dentin). *D*, Hypoplasia of the enamel resulting from a disturbance in the metabolism of calcium during the formation of the teeth. Note that only the tips of the canines and second incisors are involved in contrast with the extensive involvement of the first incisors. *E*, Leukoplakia of the tongue. *F*, Fibroma (epulis) of the buccal gingiva associated with advanced caries and periodontal disease.

Ischemic Necrosis of the Pulp. The blood supply of the pulp enters through the apex of the tooth. In trauma to the jaws the vessels may be torn. The pulp and odontoblasts undergo necrosis. In some instances inflam-

Periapical Infections—Dental Granuloma

Inflammation about the apex, bacterial or aseptic, usually results in the formation of a

mass of granulation tissue, known as a "dental granuloma."

The granuloma is soft, red, and roughly spherical, and is usually attached to the apex of the tooth. There is a loose, richly vascularized, connective tissue, with islands of squamous epithelium, derived from the rests of Malassez. Within the connective tissue are abscesses, lined in part by epithelium. There are thickening and hypercalcification of the adjacent cementum. In chronic infection nu-

bone without apparent connection with a developed tooth. The walls are composed of connective tissue with a lining of squamous epithelium.

Ameloblastoma

The ameloblastoma or adamantinoma is a tumor the histologic structure of which is similar to that of the primitive enamel organ. It occurs most frequently in the mandible

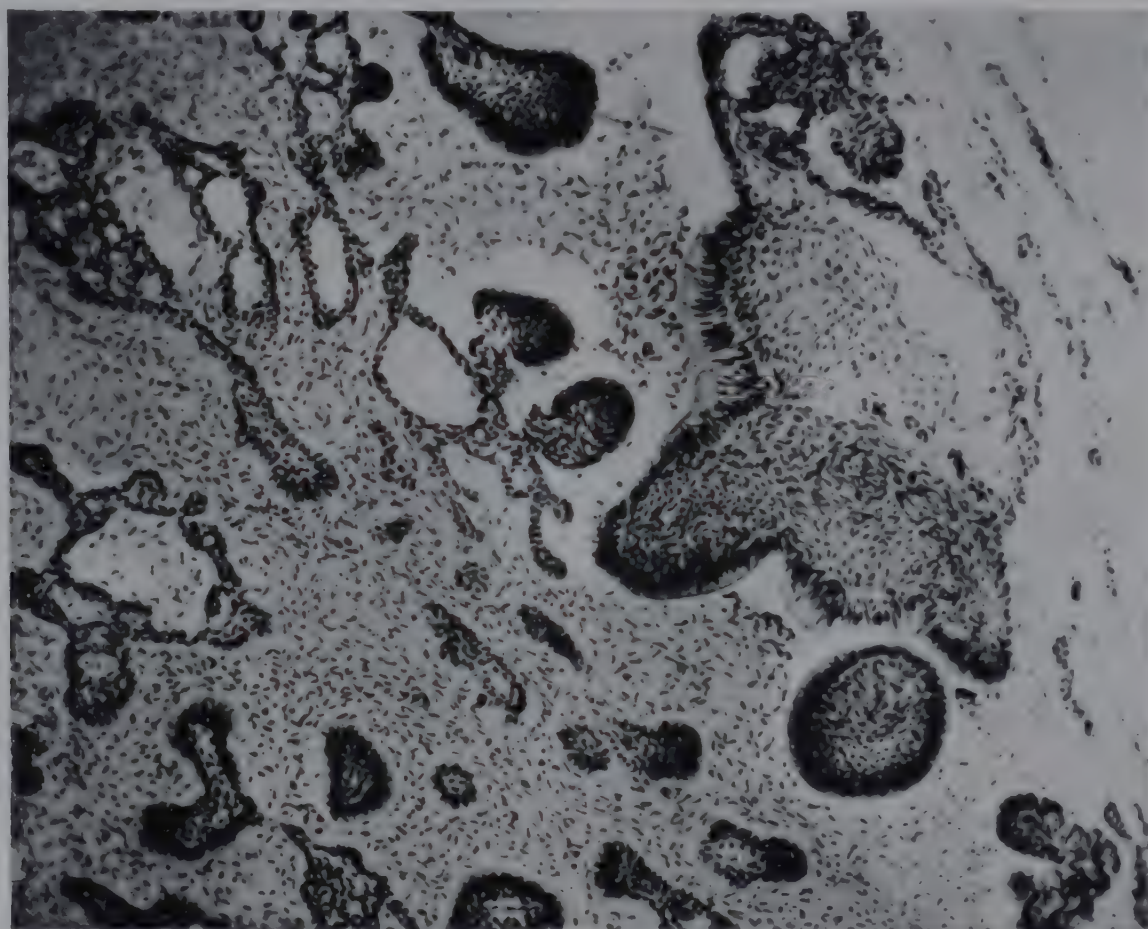


Fig. 487. Ameloblastoma of jaw. In the larger island the enamel epithelium is well shown. (Tissues by courtesy of Dr. Hamilton B. G. Robinson.)

merous fatty macrophages or cholesterol crystals may be present. The surrounding bone is resorbed. The marrow is replaced by a dense granulation. If the granuloma undergoes central liquefaction, a large sac filled with fluid forms, known as a "radicular cyst" (Hill).

Streptococcus viridans is the most common bacterium. Subacute bacterial endocarditis occasionally follows the extraction of an infected tooth.

Cysts of Dental Origin

True cysts of dental origin are derived from the stellate reticulum of the enamel organ. They may cover the crown, surround the tooth, be located on the side, or occur in the

(over 80 per cent). Ectopic ameloblastoma occurs in the region of the sella turcica and in the tibia.

Pathologic Anatomy. In general it is a circumscribed tumor within the substance of the bone, and grossly appears as soft, grayish red, cystic tissue. There is great variation in structure, but in many areas the typical structure of the enamel organ is found: a peripheral layer of columnar cells enclosing a stellate reticulum, free of blood vessels. The reticulum may undergo necrosis to form cystic spaces. The smaller nodules of epithelium may keratinize and resemble the structure of the epidermoid carcinoma. The stroma between the masses of epithelium is a loose, delicate type of mesenchyme, infiltrated with lymphocytes

and monocytes. The neoplastic property of the tumor is shown by the invasion and destruction of the surrounding bone.

Histogenesis. There seems little doubt that the mandibular and maxillary ameloblastomas are derived from remnants of the enamel organs. The hypophyseal type is probably a prosoplasia of the epithelium of Rathke's pouch to potential enamel-forming cells. The origin of the tibial ameloblastoma is obscure. It may represent a specialized type of epidermoid carcinoma (Dockerty and Meyerding).

Incidence and Causal Factors. Ameloblastomas occur with equal frequency in both sexes, and the average age of onset of symptoms is thirty years. Only two causal factors have been demonstrated, and these are questionable—rickets and chronic inflammation.

Malignant Ameloblastoma. In not over 5 per cent, there is an invasion of the surrounding tissues, or actual metastases, indicating that the neoplastic cells are malignant.

Clinicopathologic Correlation. The ameloblastoma is a slow-growing tumor, and the average lapse of time between the first symptoms and surgical removal is eight years. There may or may not be pain because of the expanding lesion within the bone. Most tumors eventually reach the gums and protrude into the mouth as a small, painful mass (Robinson). The hypophyseal tumors cause the usual signs and symptoms of increased intracranial pressure, together with the localizing signs for the sella turcica.

Odontogenic Tumors. Various combinations of epithelial and mesenchymal tumors, with or without dentin and cementum, are observed (Thoma and Goldman).

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CXVI

Diseases Peculiar to the Ear

The ear consists of three parts, the external ear, including the auricle and the external canal; the middle ear, bounded on the outside by the tympanic membrane and on the inside by the oval and round windows; and the internal ear. From a functional standpoint the internal ear is again divisible into two parts:

ing pneumatic cells of the petrous portion of the temporal bone. In severe inflammations the membranous labyrinth may be invaded. Finally infection may extend from the temporal bone to the intracranial tissues by vascular and lymphatic channels. See Chapter XXIX, page 263, on "Otitis Media."

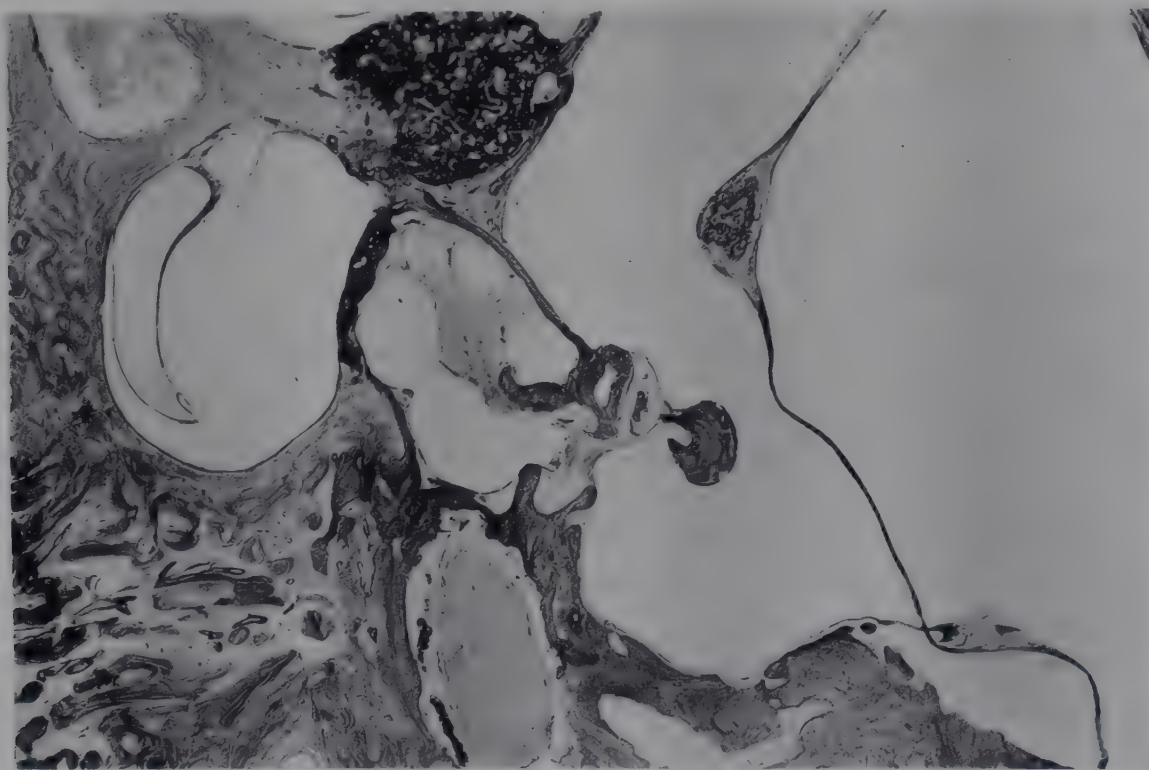


Fig. 488. Otosclerosis. (Tissue by courtesy of Dr. Theo. Walsh.)

that part concerned with the sense of hearing, and that part concerned with equilibration, mediated by the cochlea and the semi-circular canals respectively.

Normally the cavity of the middle ear is separated from the exterior by the tense tympanic membrane. After perforation, bacteria may enter and set up an inflammatory process. But bacteria enter more commonly through the eustachian tube, connecting the posterior nasopharynx with the middle ear. As a sequela of infections of the middle ear, bacteria may extend along the mucous membranes into the antrum, the mastoid, and the connect-

The structures of the ear may be affected in certain systemic diseases. In congenital syphilis deafness is one of the symptoms in the triad of Hutchinson. In acquired syphilis and in tuberculosis the temporal bone or the labyrinth may be involved. In Paget's disease the formation of new bone may encroach upon the labyrinth and result in a decrease of function.

Defects of Hearing. Deaf-Mutism. *Peripheral deafness* is induced by disease of the receptor organ, and *central deafness* results from a lesion of the nervous pathways within the cranial cavity. In *deaf-mutism* the deafness

appears early in life, so that the child never learns to speak. There are two general types: congenital and acquired. The congenital form is frequently associated with cretinism, and there is aplasia and hypoplasia of some part of the receptor organ, usually the labyrinth. The acquired type results from an inflammation of the brain or ear during the first year of life. The most common preceding diseases are: meningitis, scarlet fever, measles, diphtheria, typhoid, and mumps (Fraser).

Menière's Syndrome

Menière's syndrome, or aural vertigo, is characterized by sudden and recurrent attacks of dizziness, and by nausea, vomiting, tinnitus, and partial deafness. Pseudo-Menière's syndrome is defined as Menière's syndrome without the tinnitus and deafness. There are transition states between the two.

There are not enough pathologic studies of Menière's syndrome to give a clear description of the histologic changes. In Menière's original case there was a hemorrhagic labyrinthitis. Hallpike found dilatation of the endolymphatic system, chiefly of the scala media and saccule, degenerative changes in the organ of Corti and stria vascularis, and loss of the loose connective tissue about the saccus endolymphaticus. Dandy described some lesion of the eighth nerve in 35 per cent of patients, and believes that the basic change is in the nerve. Still other investigators believe that the syndrome results from hydration of the brain and labyrinth, with an increased pressure of the endolymph (Furstenberg, Richardson, and Lathrop); or that it is basically a vascular phenomenon associated with allergy (Atkinson).

In about 10 per cent of persons the lesions are bilateral. The mechanism of loss of consciousness with an attack of the apoplectic type of Menière's syndrome is not understood.

Otosclerosis

Otosclerosis is characterized by bilateral progressive deafness, especially for the low tones, beginning in the third or fourth decade. Pathologic changes are typical and pathognomonic. In the otic capsule there are ectopic foci of a spongy type of bone. The most common focus is at the stapediovestibular joint,

with resulting ankylosis (Fig. 488). This lesion is responsible for the deafness in most instances, as the ossicles can no longer vibrate and carry the sound waves from the tympanum to the oval window (Covell). In late stages there is a nonuse atrophy of the organ of Corti and of the cochlear nerve.

The cause of otosclerosis is unknown. In some instances the condition is familial, and when associated with osteogenesis imperfecta is clearly inherited as a mendelian dominant (Riesenman and Yater).

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CXVII

Diseases Peculiar to the Eye

The eye is one of the most complex of the organs of special sense. It is contained within a special indentation of the surface of the body, and protected by bone on all sides but one, where it is covered by the eyelid. It is connected with the brain by the optic nerve, and derives its blood supply from the intracranial vessels through the ophthalmic artery and vein.

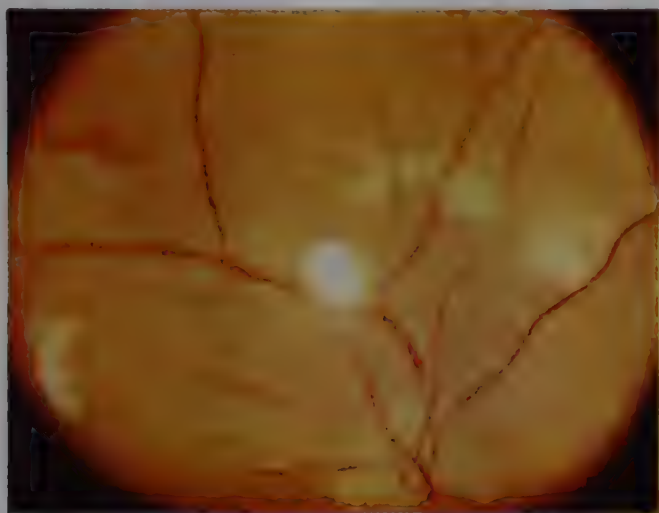


Fig. 489. Appearance of eye grounds in arteriosclerosis. (Gifford.)

Relation to Disease of the Surrounding Structures. The eye is in close proximity to the paranasal sinuses, and infection may pass from one to the other. Disease may travel along the optic nerve or in a blood vessel in either direction; thus an infection in the orbit may reach the cavernous sinus and set up a thrombophlebitis; or an arteriovenous aneurysm between the carotid artery and the cavernous sinus may cause pulsating exophthalmos. An increase of pressure within the cranial cavity is reflected in the optic disk, which bulges forward.

Relation to Systemic Disease. Examination of the eye and the tissues of the orbit frequently gives information concerning the existence of systemic disease. In many of the

purpuras, in leukemia, in syphilis, in nephritis and in arteriosclerosis (Fig. 489), and in diabetes there are changes in the structures of the eye. In Graves' disease or exophthalmic goiter the name itself indicates that there is an exophthalmos. In many bacterial diseases there is secondary involvement of the structure of the eye. Iridocyclitis is a frequent complication of rheumatoid arthritis. Hemorrhage into the retina in newborn infants is common.

Corneal Ulcer

Ulceration of the cornea is one of the common diseases of the eye. It is caused by bacterial invasion of the corneal tissues as the result of traumatic injury or a decreased resistance.

The ulcer appears grossly as a dull grayish yellow area. Microscopically a loss of the anterior epithelium and of some of the collagenous tissue of the cornea, and infiltration with polymorphonuclear leukocytes, are seen. After a few days vessels invade the cornea from the limbus, and there is conspicuous dilatation of these vessels. In severe cases the anterior chamber may fill with polymorphonuclear leukocytes, or the ciliary body and iris may become involved. If the ulceration is deep, the pressure in the anterior chamber may result in keratectasia or perforation. A serious complication of perforation is prolapse of the iris into the wound and incorporation of it into the scar. Repair is accomplished by replacement of the cornea with vascularized fibrous tissue.

Corneal ulceration is more common in adults than in children. The more important exciting causes are trauma, ulcerative bacterial inflammation, and disturbances of nutrition and innervation, as by paralysis of the fifth nerve, keratomalacia, and glaucoma.

Iridocyclitis. Uveitis

Iritis, inflammation of the iris, and cyclitis, inflammation of the ciliary body, are usually associated and designated as "iridocyclitis." When the entire uveal tract is involved (iris, ciliary body, and choroid), the term "uveitis" is used.

Acute inflammation of all or part of the uveal tract may occur as a complication of inflammation of other parts of the eye, or as an occasional manifestation of some systemic bacterial disease. There is also an agnogenic type. The pathologic changes are those of any inflammation in a loose connective tissue.

Chronic uveitis is a clinical entity occurring in young adults, having a tendency to relapse, and involving one or both eyes. It is observed as a complication of many systemic diseases, and has a positive relation to focal infection in the teeth, tonsils, and other structures. Perforating wounds may serve as the precipitating cause. The tissues of the iris and ciliary body, and to a less extent of the choroid, are edematous, hyperemic, and infiltrated with lymphocytes. There are a few giant cells. The aqueous and vitreous humors are cloudy, as the result of the passage of fibrin and cells into them from the inflamed uveal tract. Organization may lead to cataract or secondary glaucoma. A partial or total loss of vision often results from the formation of scar tissue. Sympathetic ophthalmia is a serious complication.

Sympathetic Ophthalmia

Following injury to one eye, a peculiar and characteristic inflammation of the other eye, known as "sympathetic ophthalmia," develops in from 0.5 to 5 per cent of cases.

Pathologic Anatomy. The pathologic changes in the two eyes are essentially the same. The cornea becomes opaque, and an inflammatory reaction in the iris leads to posterior synechiae, and the formation of a cataract. The aqueous and vitreous humors are cloudy. The choroid coat is thickened. Eventually there are fibrosis and contraction of the entire bulb of the eye—phthisis bulbi. There is a uniform inflammation of the entire uveal tract, characterized by a heavy infiltration of lymphocytes and epithelioid cells, the latter frequently arranged in the form of small gran-

ulomas. In the pigment layer of the choroid there are proliferation and necrosis, with the formation of small nodules known as "Dalen-Fuchs nodules." These nodules are gradually replaced by epithelioid and giant cells, with many pigment granules in the cytoplasm. A similar inflammatory reaction extends along the emissary veins into the sclera. The entire picture is not unlike that of tuberculosis.

Incidence and Causal Factors. Sympathetic ophthalmia may occur at any age. About 60 per cent of all cases follow penetrating wounds of the exciting eye; about 20 per cent follow operations on the eye; and a few are associated with intra-ocular tumors. Changes in the sympathizing eye may occur as early as ten days after injury, but are most frequently observed after three to eight weeks, and have been reported after as long as several years. No satisfactory explanation of this phenomenon has ever been made. No bacterium and no virus has ever been isolated. Although the disease has a histologic resemblance to tuberculosis, no tubercle bacilli can be isolated, and there is no evidence of tuberculosis in the lungs or in other tissues. The theory that it is an allergic response of the uveal tract has not been proved.

Clinicopathologic Correlation. The fundamental nature of the pathologic changes leads to a loss of vision in both eyes in about one-third of the cases. In two-thirds of the cases, especially those treated early, some degree of vision may be retained. Removal of the exciting eye does not invariably prevent changes in the sympathizing eye.

Glaucoma

Glaucoma is characterized by an increase of intra-ocular pressure. It may be primary, or secondary as a complication of some pre-existing disease.

Primary glaucoma is usually divided into two types: congestive glaucoma, in which there is a marked dilatation of the blood vessels of the eye and orbit, and uncongestive or simple glaucoma, which occurs without external signs and symptoms except the increased pressure. The basic change is a disturbance in the relation between the formation and absorption of the aqueous humor. In most instances there is defective absorption in the angle of the iris.

Specific pathologic changes are adhesions of the iris to the cornea at the angle and fibrosis within the angle, and consequent obliteration of the spaces of Fontana or of Schlemm's canal. As the pressure within the eye increases, there is atrophy of the retina

Cataract

A cataract is an opacity in the lens or in the capsule of the lens. Two types are recognized, developmental and degenerative. Developmental cataract results from interference

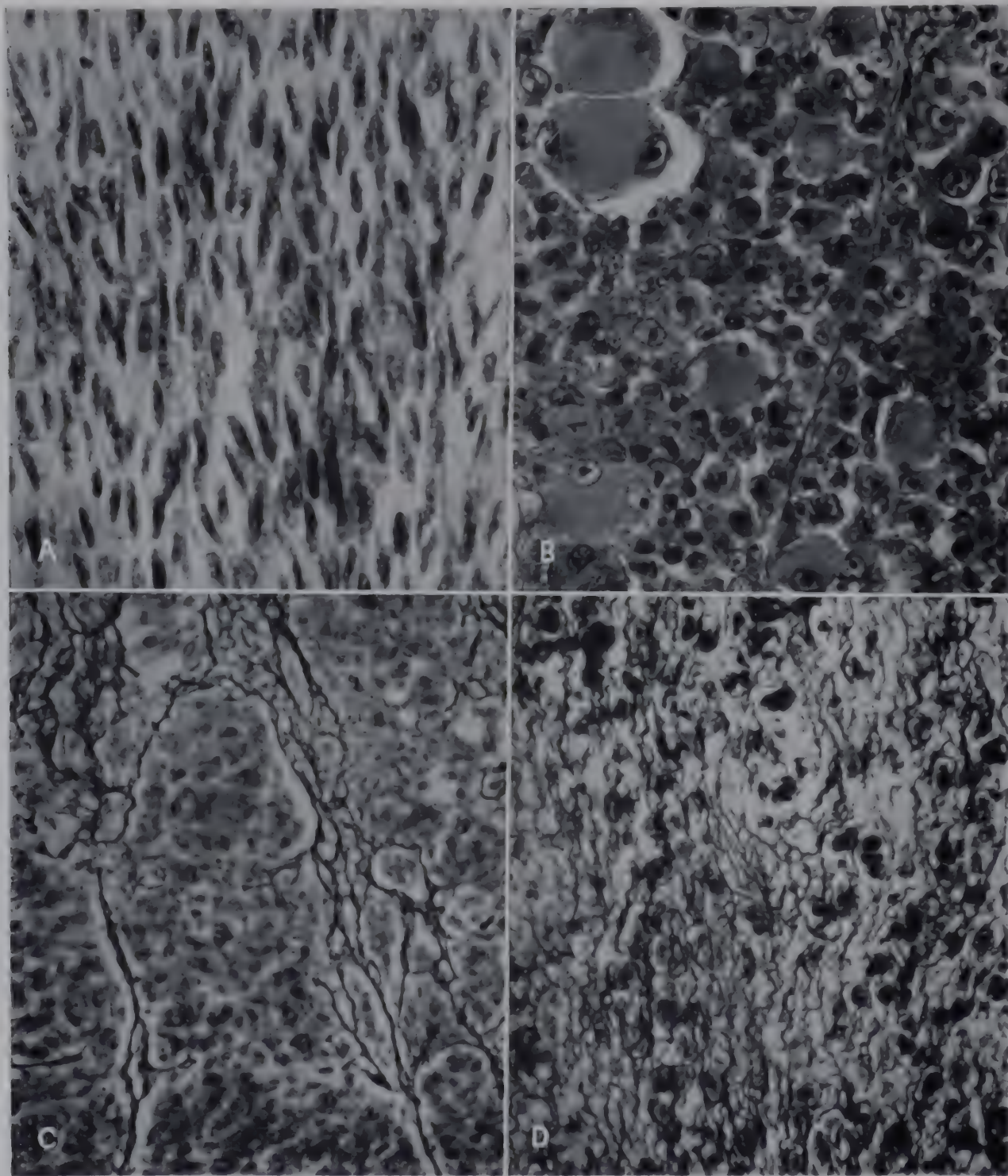


Fig. 490. Comparative photomicrographs to show the cellular type and fiber content of malignant melanomas of the eye. *A*, Spindle cell type. *B*, Epithelioid cell type. *C*, Fibers absent except in interlobular stroma. *D*, Heavy fiber content. (Photographs by courtesy of Helenor C. Wilder, Armed Forces Institute of Pathology, Neg. Nos. 72084, 72085, 63412, and 66360.)

and cupping of the optic disk. Pressure of the cup brings about atrophy of the optic nerve, with the characteristic loss of peripheral vision, and scotomas.

Glaucoma is a disease of the middle and late years, more common in persons with hyperopia. It runs a long course and usually involves both eyes. The ultimate result is a loss of vision.

with the normal development of the lens by hereditary, nutritional, or inflammatory processes. Included in this type are anterior and posterior polar, central, zonular, coronary, punctate, congenital, and juvenile cataract. Degenerative cataracts are caused by retrogressive changes in the fully developed tissue. In this category are senile nuclear and cortical cataracts, cataracts resulting from radiant

energy and trauma, and those associated with systemic disease. Senile cataract is the most common type, and is seen after the age of fifty years. Both eyes are affected, and the opacity may be in the nucleus or the cortex. The earliest change is the separation of the fibers of the lens by small droplets of fluid—morgagnian spherules. Later the fibers in the affected region swell, become vacuolated, and gradually undergo autolysis, producing a cavity filled with a soft mass of disintegrated

spaces along the optic nerve and may appear within the cranial cavity. It ruptures through Bruck’s membrane and fills the vitreous. In terminal stages there are perforation at the sclerocorneal junction and the formation of a black necrotic tumor mass on the anterior surface of the eye. Occasionally the tumor is distinctly infiltrative and forms an almost uniform thickening of the entire uveal tract. Widespread metastases occur and are most abundant in the liver. About one-fourth of the

TABLE 60. PROGNOSIS IN RELATION TO HISTOLOGIC TYPE AND FIBER CONTENT

Cellular Type	Per Cent Dead within 5 Years	Fiber Content	Per Cent Dead within 5 Years
Spindle A.....	6	No fibers.....	80
Spindle B.....	25	Less than 50 per cent.....	55
Fascicular.....	38	About 50 per cent.....	44
Epithelioid.....	49	More than 50 per cent.....	36
Mixed.....	71	Fibers in all areas.....	10

fibers, fat, and albuminous fluid. In the late stages calcification and shrinkage of the lens may occur.

Secondary cataracts or occupational cataracts follow exposure to radium or x-rays, electric shock by a high voltage current or lightning, exposure to high occupational temperatures, various diseases of the eye, various systemic diseases such as diabetes, tetany, and primary muscular dystrophy, and dinitrophenol and naphthalene poisoning.

Some congenital cataracts occur in children whose mothers had rubella during the first three months of pregnancy.

primary tumors show extensive necrosis, and accurate histologic study is difficult.

Histologic Types and Prognosis. Wilder and Callender have classified the tumors into five cellular types:

- Spindle A:* The nucleus has a delicate reticular structure with an ill-defined or indistinguishable nucleolus.
- Spindle B:* The nucleus contains a rather coarse network and a prominent nucleolus.
- Fascicular:* In this type the cells are arranged in parallel bundles, and each cell is of the Spindle B type.
- Epithelioid:* The cells are round or polygonal, large, and show variation in size and shape. The nucleus is large, round, with a prominent nucleolus.
- Mixed type:* In this type two or more of the other varieties of cells are admixed. The most usual combination is of Spindle B and epithelioid cells.

The amount of reticulum separating the tumor cells has also been evaluated by Wilder and Ash, and the prognostic import of an evaluation of the relative amount of reticulin fibers and the type of cell is well shown in Table 60.

In general the deeper the pigmentation the less malignant the tumor (Benedict).

Incidence and Causal Factors. The malignant melanoma of the choroid constitutes less than 0.06 per cent of all ocular disease. It occurs equally in both sexes, and the average

Malignant Melanoma of the Uveal Tract

Pathologic Anatomy. The malignant melanoma of the choroid first appears as an elliptical or lenticular shaped tumor in the outer layers of the choroid. This characteristic shape results from pressure of the sclera on the outside and of Bruck’s membrane on the inside. On the inner surface of the eyeball there is a nodular, gray-black, projecting mass, made up of a black, granular or fibrillar, moderately firm tissue. With further growth the tumor penetrates through the vascular channels in the sclera and invades the soft tissues of the orbit. It follows the lymphatics and vascular

age of onset is fifty years. The two eyes are affected with equal frequency, and rarely the tumor is bilateral. A familial tendency is oc-

TABLE 61. HISTOLOGIC TYPES AND PROGNOSIS

	Neuro- epitheliomatous Type	Retino- blastomatous Type
No. of cases traced...	16	16
No. living without recurrence.....	9	2
Died of other causes.	1	0
Died of recurrence...	0	1
Died of glioma.....	6	13
Per cent good results.	62½	12½

casionally evident. There is little positive evidence concerning cause.

Other Tumors of the Uveal Tract. Nevi of the choroid and of the iris are rare and may

Glioma of the Retina

The usual specimen of glioma of the retina seen by the pathologist or ophthalmologist is a gray, friable tumor mass partially or completely filling the vitreous. It is firmly attached to and an integral part of the retina. The neoplastic tissue is granular, grayish yellow, and friable, with numerous foci of necrosis, hemorrhage, and calcification. In late stages the tumor tissue invades through the sclera and along the optic nerve into the cranial cavity (Weller).

Histologic Types and Prognosis. There are two general types of the glioma of the retina. In the more common variety, small, round or polygonal, hyperchromatic cells are arranged as pseudorosettes about small blood vessels. Between these circular masses the tissue is edematous, hemorrhagic, and necrotic. Some investigators designate this type as the “neuro-epitheliomatous type” of glioma. In the second

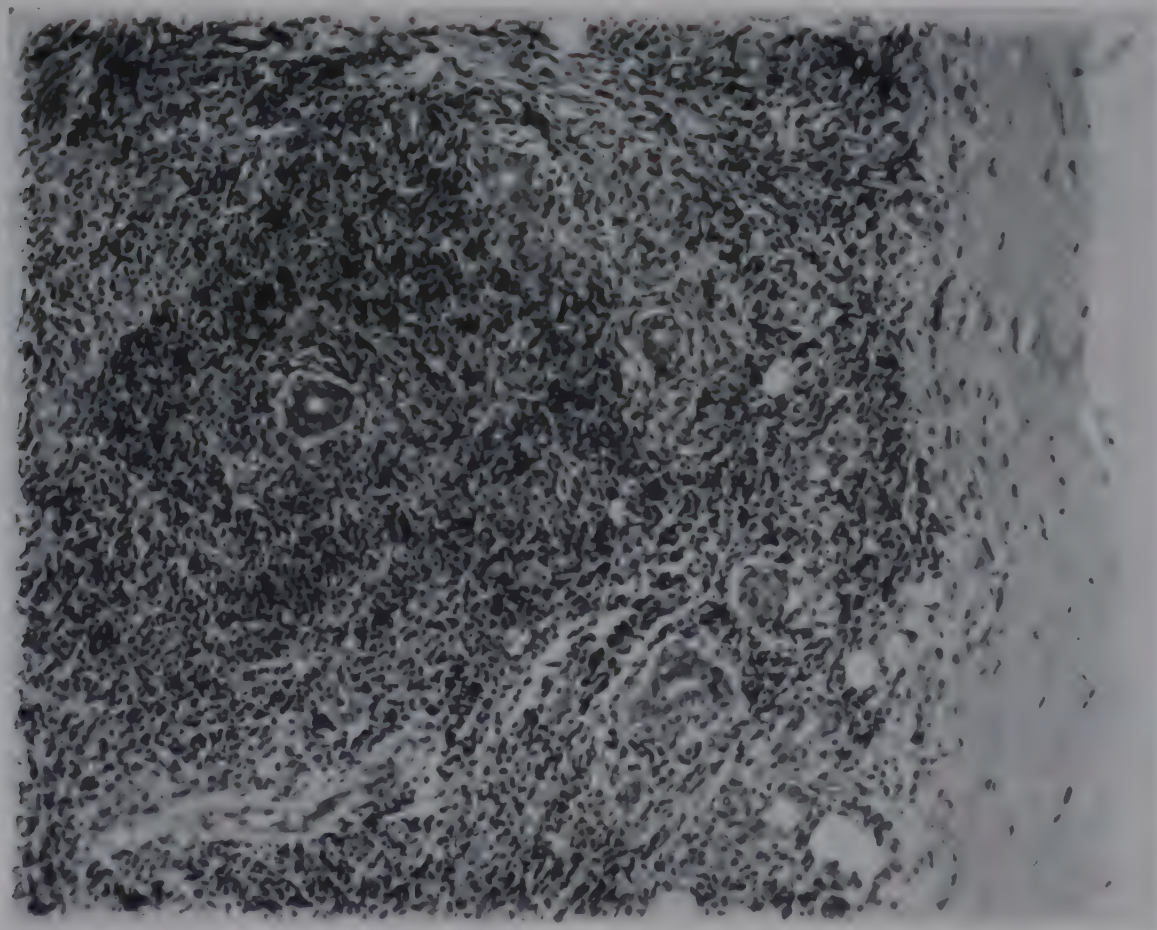


Fig. 491. Mikulicz's disease of the lacrimal gland.

be associated with nevi or neurofibromas of the skin. Similarly the malignant melanoma of the choroid is occasionally found in a patient with von Recklinghausen's disease (Gartner). Other types of neoplasia include the myoma, angioma, and neurofibroma. Metastatic carcinoma is uncommon.

type the perivascular arrangement is not evident, but the somewhat smaller, less chromatic cells are irregularly arranged in a solid mass, with occasional cells grouped as a true rosette with a mat of fibrils in the center of the circle. This is designated as the “retinoblastomatous type” of glioma. The justification for this divi-

sion into type is supported by the difference in prognosis as shown, in the figures of Parkhill and Benedict (Table 61).

Histogenesis. The most common site of origin is the ciliary portion and the posterior segment of the retina. In many, multiple nodules appear in various parts of the retina. The exact cell of origin is not known, but a malformation of the cells of the inner nuclear layer has been observed (Ch'in). The occurrence of a typical astrocytoma of the retina suggests that tumors of the retina may, when fully studied, show the same variation and mixture as tumors of the brain.

Incidence. Glioma of the retina is distinctly a disease of young children. It may be present at birth and only rarely appears after the age of six. It is estimated to occur in one of each 34,000 live births. Many examples of it are definitely familial. It is bilateral in 20 per cent. Other examples are apparently sporadic. Relatively few cases have been observed in the Negro race. The mechanism of heredity is not clear (Weller).

Miscellaneous Diseases of the Eye

Chalazion. This is a chronic inflammation of one of the meibomian glands and the surrounding tissue in consequence of occlusion of the duct. A firm spherical nodule in the lid adheres to the tarsus but not to the skin. There are dilatation of the ducts, atrophy of the acini, fibrosis, infiltration with lymphocytes, and the formation of giant cells. The result is a single cystic cavity surrounded by dense fibrous tissue.

Mikulicz's Disease. This is a clinical and pathologic entity characterized by benign, symmetrical, and painless enlargement of the salivary and lacrimal glands. The glands preserve the usual shape and are not adherent to the surrounding structures. On section the greater part of the glandular elements are seen to be lost and the surface has a uniform, gray, finely granular appearance. The epithelial acini are atrophic and widely separated by masses of lymphoid tissue (Fig. 491). The interlobular septa are fibrotic (Lehman and Leaman). There is no essential pathologic change in the remainder of the body. The cause is unknown, but the condition has been reported in families.

Mikulicz's Syndrome. In a variety of dis-

eases, especially lymphoid leukemia, lymphosarcoma, and Hodgkin's disease, there may be enlargement of the lacrimal and salivary glands simulating the clinical and pathologic picture of Mikulicz's disease. This represents nothing more than participation of these structures in a generalized disease.

Dacryocystitis. Inflammations of the lacrimal sac are usually associated with obstruction of the nasolacrimal duct by a chronic inflammation of the nasal mucosa or at the inner canthus of the eye. In acute inflammations the surrounding tissue is affected and the drainage of the coronary vein from the side of the nose into the cavernous sinus must be borne in mind in evaluating the seriousness of the condition.

Pterygium. In this condition, more common in elderly persons and in those exposed to the elements, a triangular fold of vascularized opaque connective tissue extends from the inner or outer canthus to a point on the surface of the cornea.

Arcus Senilis. This is a common lesion of older persons and appears grossly as a white or gray opaque ring just within the sclero-corneal junction, and separated from the sclera by a thin, clear zone. The cause is unknown.

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CXVIII

Diseases Peculiar to the Skin

Most diseases of the skin can be arranged according to the basic pathologic change into five types: atrophy, hypertrophy, abnormalities of the pigment distribution, inflammation, and neoplasia. Only a few of the many hundreds of dermal lesions described in textbooks on diseases of the skin can be discussed here. Some diseases are a part of systemic conditions, and have been discussed in other chapters. The most important conditions in which the pathologic changes are limited to the skin will be described in the following two chapters.

Atrophy of the Skin

As man grows old there is a progressive loss of the tissues of the skin. The epidermis is thinner, and the rete pegs are less conspicuous or absent. Elastic fibers of the dermis are lost, and collagen becomes denser.

Lichen Sclerosus et Atrophicus. The characteristic lesion of lichen sclerosus et atrophicus is an irregular, flat-topped, white papule, which may be discrete or one of a group forming a plaque. The orifices of the hair follicles and sweat gland ducts, distended with keratin, appear as small horny plugs on the surface of the papule. Later, with the occurrence of atrophy, the skin has a wrinkled, tissue-paper-like appearance. Microscopically, although the epidermis is atrophic and the rete ridges are obliterated, there is hyperkeratosis with keratotic plugging of the hair follicles. In the upper dermis edema is so pronounced that small vesicles form at the dermal-epidermal junction. In the mid-dermis a lymphocytic infiltrate is present. No obliterative changes are found in the blood vessels.

Pseudoxanthoma Elasticum. In this condition, there are symmetrical, yellowish brown, flat papules, arranged discretely or in netlike groups on the covered parts of the body and

less commonly on the mucous membranes. Microscopically the elastic fibers are intertwined, swollen, and fragmented in irregular areas (de Sá Penella and Esteves). There is a slight infiltration with mast cells. In about 25 per cent of cases, there are peculiar angioid streaks in the retina (Wagener). Vascular hypertension and degeneration of the elastica of the arteries have been found as associated conditions. The cause appears to be a basic defect in the elastic tissues, not inherited.

Hypertrophy of the Skin

Ichthyosis. In this condition the skin, particularly on the extensor surfaces of the extremities, is dry, scaly, and tense, hence the name "ichthyosis" or "fish skin." Microscopically the basal layer is intact and contains numerous dividing cells and pigment granules. The stratum granulosum is absent. The rete pegs are atrophic. The hair follicles are plugged and frequently cystic. The sweat glands and sebaceous glands are inconspicuous and atrophic. Mild forms of the condition are designated as "xeroderma." Most instances of ichthyosis are congenital, and are present at birth or appear shortly thereafter, but rarely ichthyosis occurs in adult life following some infectious disease.

Verruca Vulgaris (Common Wart). The common wart is caused by a species-specific, epitheliotropic virus, and is characterized by a circumscribed hypertrophy and hyperplasia of the epidermis with thickening of the horny layer. Several clinical types are recognized: verruca vulgaris (hard wart), verruca plana juvenilis (flat wart), verruca plantaris (plantar wart or papilloma), verruca or condyloma acuminatum (venereal wart), and verruca filiformis (pedunculated wart).

Pathologic Anatomy. The pathologic

changes are pathognomonic: hyperkeratosis, acanthosis, and hypertrophy of the rete over a circumscribed area. Secondary inflammation is not uncommon. The rete are elongated and widened. Mitoses are abundant and the individual cells are large.

Incidence. Warts reach highest incidence between the ages of ten and thirty, and are distributed about equally in the two sexes. Satellite warts about the original lesion or on other parts of the body are common, and rep-

acanthosis and hyperkeratosis with keratin cysts and islands of dermis in the epidermis.

Disturbances of Pigment Distribution

The normal color of the human skin is a mixture of five pigments: melanin, melanoid, carotene, and reduced and oxyhemoglobin (Jeghers).

Vitiligo. This condition is a disturbance in the pigment metabolism, in which oval or ir-

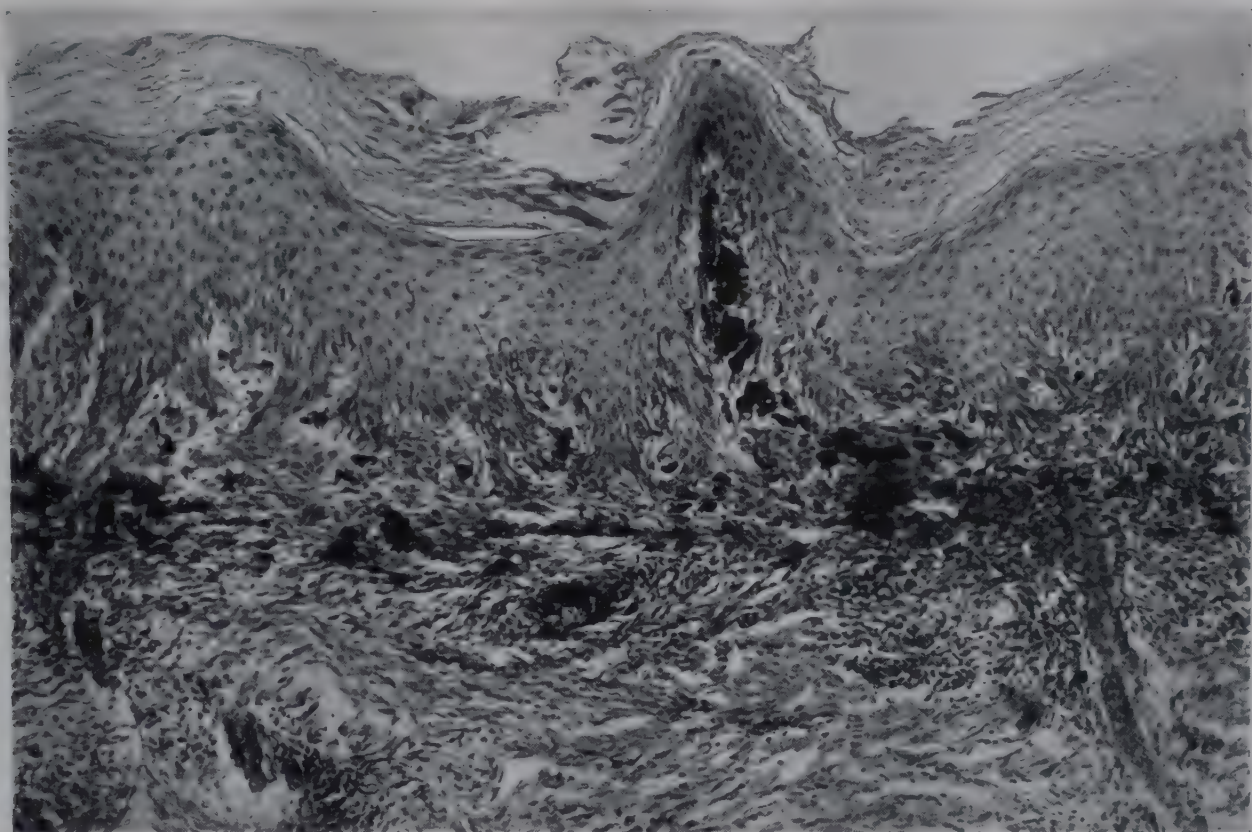


Fig. 492. Xeroderma pigmentosum. The epidermis shows hyperkeratosis. There is irregular proliferation and prolongation of the rete pegs. Over the dermal papilla the spinous layer of the epidermis is atrophic. Melanin pigment is increased in the basement layer of the epidermis. Numerous chromatophores laden with pigment are present in the dermis. (Photography by courtesy of Dr. Zola Cooper.)

resent auto-inoculation. All types are probably caused by the same virus, but objective proof of this for the plantar wart has not been submitted. The incubation period in experimental inoculation may be as long as six months (Rulison).

Callus. Clavus. Microscopically the callus shows an increase in the thickness of the stratum corneum and slight thickening of the stratum lucidum and stratum granulosum. The clavus or corn is a callus in which the keratinization is highly developed in the center as a dense plug.

Seborrheic Keratosis. The senile wart is a round, brown thickening of the epidermis, covered by greasy matter, and found most frequently on the trunk. Microscopically there is

regular areas of skin become white. Microscopically there is an absence of pigment and of dopa-positive cells in the basal layer. The epidermis is atrophic and there is a slight infiltration of lymphocytes and pigment-containing chromatophores in the dermis. Symptomatic and primary types are recognized (Fig. 12, p. 23).

Xeroderma Pigmentosum. This lesion is of interest because of the frequent development of a malignant tumor in it. The first change usually appears before the second year of life, and is an erythema of the face, neck, and arms following exposure to sunlight, which persists longer than usual. This is followed by hyperpigmentation, frequently focal, in the form of dark freckles. Hyperemia of the con-

conjunctiva and photophobia appear. The epidermis is atrophic and hyperkeratotic until by the sixth or seventh year there are hard, warty elevations from which epidermoid carcinoma starts and invades the underlying tissues (Montgomery and Reuter). The disease is usually fatal by the twentieth year of life. It is inherited as a simple recessive and several siblings of the same family may be affected (Macklin). It is possible that the basic defect is an inherited sensitivity to ultraviolet rays.

leave no mark except occasional slight pigmentation. The clinically uninvolved skin is not normal, since injury during an acute phase of the disease will result in the localization of a plaque—Koebner phenomenon. The cause is unknown. Two or more members of a family are frequently affected.

Lichen Planus. In this disease, there are elevated, glistening, yellowish-red or bluish-red umbilicated papules, from 1 to 3 mm. in diameter, in the skin. There are hyperkeratosis, thickening of the stratum granulosum,

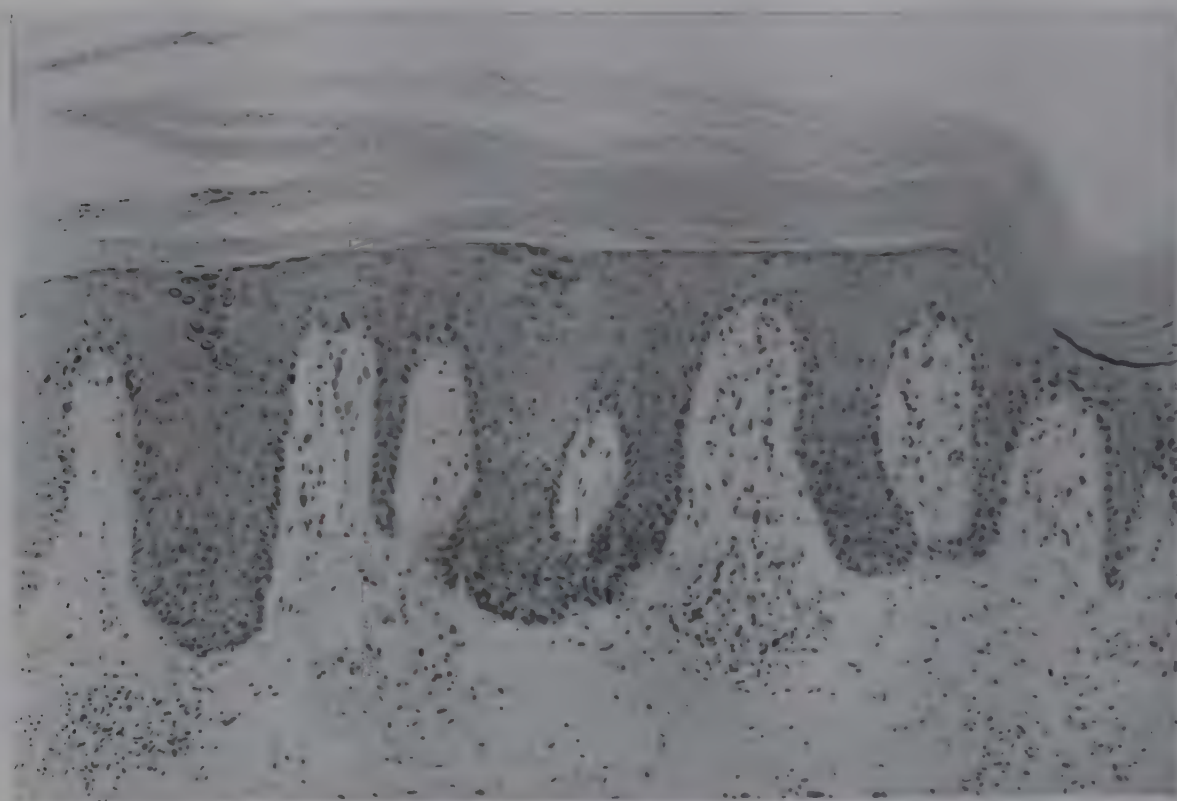


Fig. 493. Skin in psoriasis. The epidermis shows marked parakeratosis, absence of the stratum granulosum, and elongated, "test-tube-like" rete pegs. Munro's abscesses—small collections of leukocytes in the parakeratotic scale—are present. The infiltrate in the dermis is slight in amount and made up of lymphocytes. (Photograph by courtesy of Dr. Zola Cooper.)

Nonspecific Inflammations of the Skin

Psoriasis. Psoriasis is a chronic and recurrent disease, characterized by the development of red papules and plaques covered by silvery white scales. In the early stages the epidermis is edematous and the rete ridges are widened. The blood vessels are dilated and there is a slight infiltration with lymphocytes and a few leukocytes (Fig. 493). In the late stages, the stratum granulosum is entirely absent, and there is conspicuous parakeratosis. Within the stratum corneum there are focal collections of leukocytes.

The lesions are most common on the extensor surfaces, and are frequently symmetrical. Persons of all ages and both sexes are affected, and the course extends over months and years. After disappearance the lesions

conspicuous keratohyaline granules, flattening of the rete, and a heavy infiltration of lymphocytes into the papillary layer of the dermis. The epidermis is generally edematous and infiltrated with a few lymphocytes and leukocytes (Fig. 494).

Lichen planus is most common in young adults, and lesions are most frequently found on the flexor surfaces of the wrists and forearms and inner aspects of the knees and thighs. The cause is unknown (Baird).

Urticaria. The typical lesion of urticaria, a wheal, is a pale pink or red, elevated plaque that itches intensely. In the acute phase, there is extreme edema of the epidermis without cellular infiltration. In the chronic form, there are subpapillary infiltrations with lymphocytes, plasma cells, leukocytes, and mast cells, and increased pigmentation in the basal layer

of the epidermis. Urticaria is usually the dermal expression of allergy, but in susceptible persons irritation of the skin will provoke a wheal.

Urticaria Pigmentosa. Urticaria pigmentosa may occur in either children or adults, and unless some other condition supervenes rarely produces death. Within the skin there are firm, elevated, red macules, or rarely vesicles, which on microscopic examination prove to be an infiltration of the dermis with mast cells. The overlying epidermis is atrophic and shows

fold types of erythema, although classified and named on the basis of the dermal lesions, are manifestations in the skin of systemic disease. The discussion in this section will be confined to the type of erythema which is a distinct entity. This type is best designated as "erythema exudativum multiforme of Hebra."

Pathologic Anatomy. The initial lesions of the skin are usually symmetrical, red or bluish papules that later develop into vesicles. Conspicuous edema of the papillary bodies, swelling of the collagenous fibers, dilatation of the

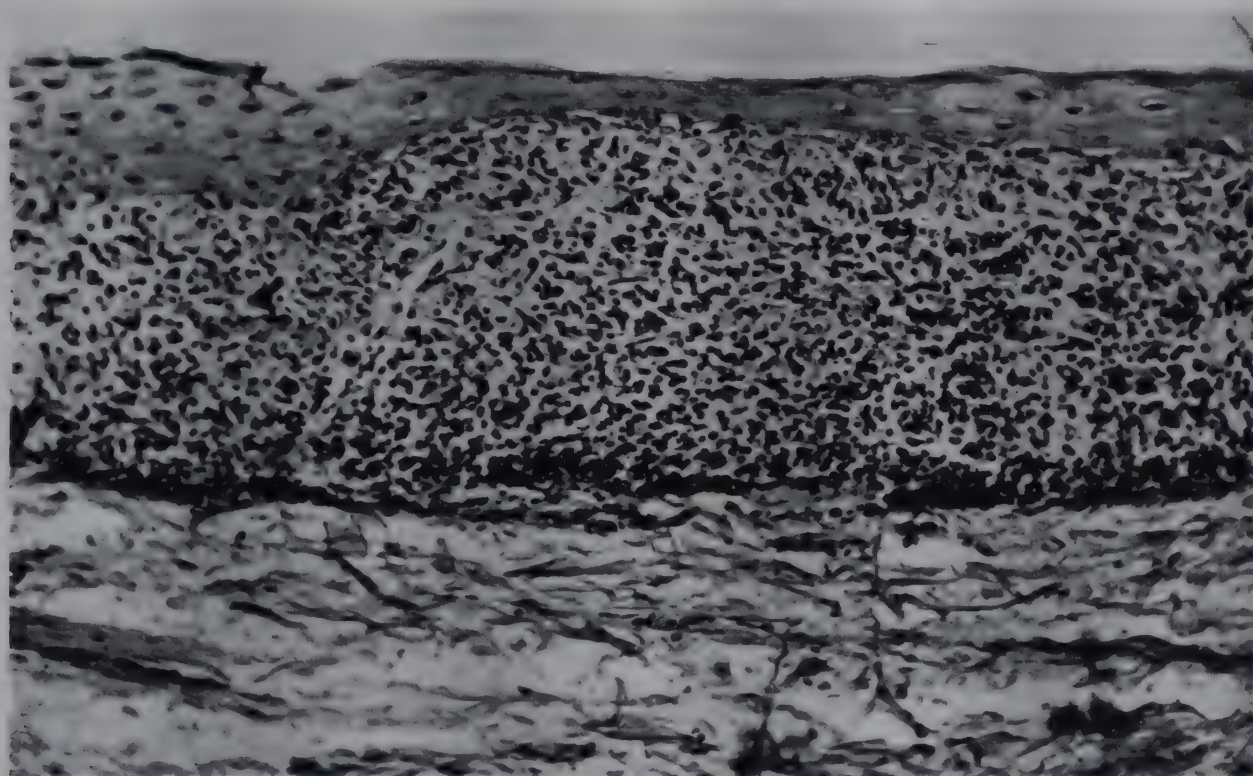


Fig. 494. Lichen planus. The epidermis is atrophic. The basement membrane of the epidermis is not clearly demarcated, and areas of liquefaction necrosis are present in the basal layer. A massive, sharply delimited cellular infiltrate, made up uniformly of lymphocytes, is present in the upper third of dermis. (Photograph by courtesy of Dr. Zola Cooper.)

hyperkeratosis and parakeratosis. Focal collections of mast cells are also found in the spleen, lymph nodes, and thymus. The cause is unknown.

Acrodynia. This condition of children is characterized by swelling and redness of the hands, together with certain systemic changes, such as loss of weight and appetite, weakness, irritability, paresthesias, paresis, elevation of the blood pressure, and loss of hair and teeth. In the skin there is an advanced degree of hyperkeratosis and acanthosis. In the dermis there are slight edema and proliferation of capillaries without cellular infiltration. In the viscera there is little except hyperplasia of the lymphoid tissue. Degeneration in nerves has been reported (Warthin). The cause is unknown, and the prognosis is good.

Erythema Multiforme. Many of the mani-

fold types of erythema, although classified and named on the basis of the dermal lesions, are manifestations in the skin of systemic disease. The discussion in this section will be confined to the type of erythema which is a distinct entity. This type is best designated as "erythema exudativum multiforme of Hebra."

Pathologic Anatomy. The initial lesions of the skin are usually symmetrical, red or bluish papules that later develop into vesicles. Conspicuous edema of the papillary bodies, swelling of the collagenous fibers, dilatation of the blood vessels, proliferation of the capillary endothelium, and an advanced perivascular infiltration of lymphocytes and a few leukocytes are seen microscopically. In older lesions, there are edema of the epidermis and the formation of intra-epidermal vesicles. The cellular infiltration is composed largely of polymorphonuclear leukocytes, and the vessels are tremendously dilated. Hemorrhage is present. Similar lesions occur on the mucous membranes of the respiratory and alimentary tracts and in the conjunctiva.

The pathologic lesions in the viscera have not been accurately described, as the mortality is low. From a clinical standpoint, the systemic alterations are an acute inflammation of the pharynx, enlargement of the lymph nodes and spleen, pain in the joints, and albuminuria and hematuria. It has been sug-

gested that the basic pathologic change is damage to capillary vessels with resultant thrombosis, hemorrhage, and inflammation (Keil).

Incidence. Erythema multiforme occurs at all ages, but is more common in young adults. The sites of predilection are the sides of the face and neck, dorsal surfaces of the hands and forearms, the legs, and dorsal surfaces of the feet. Recurrence is the rule, and each attack lasts from ten to fourteen days.

Causal Factors. The systemic signs and symptoms of sore throat, fever, and enlarge-

ment of the lymph nodes and spleen suggest an infectious disease, but no bacterium or virus has been consistently recovered. In a few patients there is an apparent association with herpes labialis and herpes zoster. A considerable number of attacks are provoked by exposure to sunlight, and allergy is also a possible factor.

Pemphigus. Originally all diseases of the skin in which bullae formed were designated as pemphigus. Recently, the term has been reserved for a certain type of bullous lesion. The disease is characterized by the formation of bullae filled with clear or cloudy fluid, which rupture and form scabs. The bullae may be discrete or confluent, and are often sym-

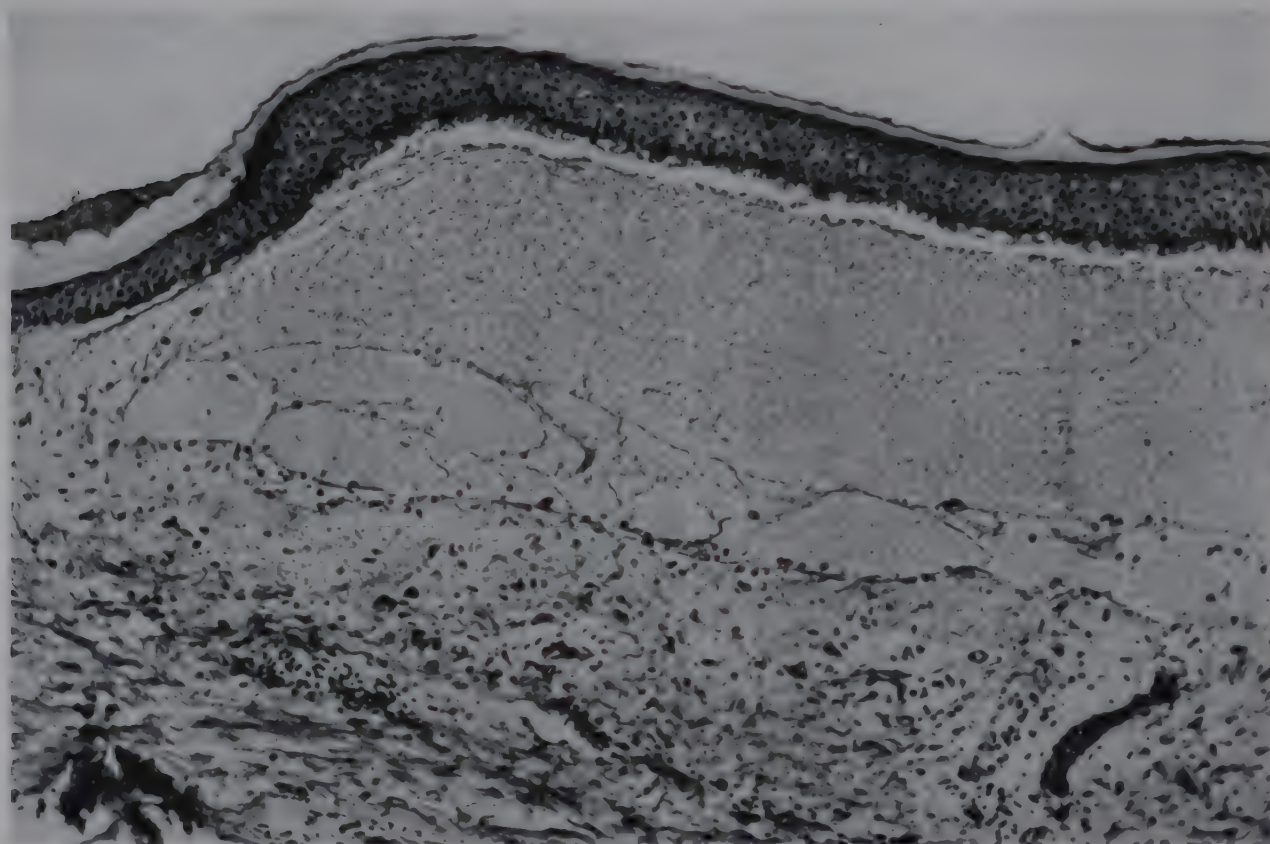


Fig. 495. Pemphigus. A large unilocular bulla filled with coagulated serum, traversed by strands of fibrin, has separated the epidermis from the dermis. The dermis is edematous, and an infiltrate of lymphocytes and eosinophils is present. (Photograph by courtesy of Dr. Zola Cooper.)

ment of the lymph nodes and spleen suggest an infectious disease, but no bacterium or virus has been consistently recovered. In a few patients there is an apparent association with herpes labialis and herpes zoster. A considerable number of attacks are provoked by exposure to sunlight, and allergy is also a possible factor.

Dermatitis Herpetiformis. Dermatitis herpetiformis is a chronic relapsing inflammation of the skin characterized by the appearance of symmetrical erythematous, papular, vesicular, bullous, and pustular lesions. The sacral triangle and the scalp are most frequently involved. An attack is usually preceded by mild systemic symptoms. The microscopic picture varies with the type of eruption. There are

metrically arranged over the surface of the body. Microscopically, inflammation of all layers of the skin is observed. The blood vessels of the dermis are dilated and there is edema of the connective tissue, which is moderately infiltrated with lymphocytes, mononuclear cells and an occasional polymorphonuclear leukocyte. The bulla is seen histologically as the accumulation of fluid either between the stratum corneum and the rete or between the epidermis and the dermis. The fluid frequently contains a sufficient amount of fibrinogen to form a delicate network of fibrin (McCardle, Baumberger, and Herold). Gross and histologic changes in the internal viscera are inconspicuous and inconstant. Death is caused by exhaustion or by a sec-

ondary infection with staphylococci and streptococci. In the latter case, abscesses or bronchopneumonia may be found in the viscera.

Varieties. It is customary to recognize four varieties of pemphigus: acute pemphigus, pemphigus vulgaris, pemphigus foliaceus, and pemphigus vegetans. Acute pemphigus runs a rapid course and is observed most frequently in butchers or following bites by animals, or vaccination. It has been suggested that it is related to hoof and mouth disease of cattle. Pemphigus vulgaris is the usual variety. The bullae develop suddenly on an apparently normal skin, and contain a serous, purulent or hemorrhagic fluid. Following rupture and crusting of one group of lesions, the patient is free from disease for a period of weeks to months, when another group forms in the same or in another area. In pemphigus foliaceus the bullae develop rapidly and are filled with pus. They rupture, leaving a raw, moist, surface. The temperature frequently increases, and the hair and nails may be lost. In pemphigus vegetans the lesions persist, and condyloma-like granulations grow out from the base of the ulcers, especially in the moist folds of the body (Gellis and Glass).

Causal Factors. The etiology of pemphigus is unknown. No bacterium or virus has been established as the cause of the disease (Eberson; Markham and Engman). The theory that pemphigus is a toxic reaction (Pels and Macht) and the theory that it is neuropathic are based on inconclusive evidence.

Nodular Subepidermal Fibrosis. This lesion has been variously designated as dermatofibroma, histiocytoma, and sclerosing hemangioma. The lesion is a freely movable firm, gray to brown, round or ovoid nodule 5 to 30 mm. in diameter. Multiple lesions are common. Microscopically there is a cellular dense fibroblastic tissue with thin walled vessels and a few to abundant mononuclear cells containing hemosiderin and fat (Rentiers and Montgomery).

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CXIX

Tumors of the Skin

The skin is in an exposed position and hence subject to many hazards of the environment. Likewise diseases and tumors of it are readily accessible for diagnosis and treatment.

In the skin, in addition to epithelium and mesodermal tissues there are many specialized tissues. Tumors may be derived from any of the cells.

both preponderantly diseases of men as shown in Table 62, taken from Schrek.

About 30 per cent of all persons with a cutaneous carcinoma have a second cutaneous carcinoma, or a malignant tumor of some other tissue of the body (Warren and Hoerr).

Causal Factors. Many causal factors or associated lesions of cutaneous carcinoma are

TABLE 62. SITES OF ORIGIN OF CUTANEOUS CARCINOMA

Site of the Carcinoma	Basal Cell Carcinoma		Epidermoid Carcinoma	
	Males	Females	Males	Females
Upper part of the face.....	280	221	128	75
Nose.....	183	112	60	43
Lower part of the face.....	115	76	58	23
Ear.....	161	65	225	33
Scalp.....	18	27	9	15
Neck.....	50	37	51	15
Trunk.....	49	54	24	44
Upper extremity.....	29	23	153	65
Lower extremity.....	10	17	22	16
Totals.....	895	632	730	329
	1527		1059	

General Aspects of Cutaneous Carcinoma

There are two important types of carcinoma of the skin: epidermoid carcinoma and basal cell carcinoma. Carcinomas of the mucocutaneous junction—carcinoma of the lip and carcinoma of the anorectum—are discussed in the chapters on the alimentary tract (pp. 639 and 679). There will be considered here only those tumors arising in the epidermis of the surface of the body.

Incidence. The average age of onset of epidermoid carcinoma is sixty-eight years and of basal cell carcinoma sixty years. They are

known. The exposed parts of the skin are more commonly affected in the white race than the colored race, while the unexposed parts show no difference. In the southern states of the United States skin cancer is about one-third of all cancer while in the North it makes up only about a seventh.

The origin of epidermoid carcinoma in scars of previous injury (Schrek), in chronic sinus tracts, and in the scars of burns from radium and x-ray (Cole) all suggest the role of chronic irritation. Similar evidence is given by the occurrence of carcinoma in those who clean chimneys in England, in the mule spinners who get oil on their clothes (Southam;

Kennaway), in those exposed to fluids containing arsenic as sheep dippers (O'Donovan), and in the tribesmen of Kashmir who wear hot bricks next to the abdomen (Neve).

Precancerous Lesions. There are certain diseases of the skin in which carcinoma develops. Xeroderma pigmentosum has already been mentioned and discussed. In malignant lentigo, pigmented spots, usually on the face, appear in older persons. After months or years

neck, back, and scrotum. Microscopically the cyst is lined by squamous epithelium. In the surrounding fibrous tissue there are remnants of the sweat glands. Either basal cell or epidermoid carcinoma may begin in the epithelial lining of not more than 3 per cent of sebaceous cysts. After many years a carcinoma may develop in the lesions of Bowen's disease (Fig. 496), and of acrodermatitis chronica atrophicans (Pack and Wuester).



Fig. 496. Bowen's disease. The epidermis shows hyperkeratosis and parakeratosis. The granular layer is absent. The spinous layer is thickened, and scattered through this layer are many large vacuolated cells with pyknotic nuclei. In places these cells are fused to form the so-called "Bowen's cells" or "basket cells." In the dermis there is a marked inflammatory infiltrate. (Photograph by courtesy of Dr. Zola Cooper.)

the spots become confluent, and the underlying tissue is indurated. Microscopic section will reveal a typical cutaneous carcinoma, either basal cell or epidermoid (Shaw). Keratoses are of two types: senile and seborrheic. The senile variety are most frequently located on the exposed parts of the body and about 5 per cent become carcinomatous. Seborrheic keratosis is more common on the trunk, and very few instances develop into malignant tumors (Eller and Ryan). Cutaneous horns and follicular keratosis (Darier's disease) occasionally are the site of origin of an epidermoid carcinoma (Charache). Rarely an epidermoid carcinoma may arise in one of the lesions of hereditary palmar and plantar keratosis. The sebaceous cyst or wen is formed by dilatation of the sebaceous glands following occlusion of the duct. It is most common on the scalp,

Prognosis. The prognosis in the two types of cutaneous carcinoma differs, depending upon clinical malignancy and histologic malignancy. The basal cell carcinoma does not metastasize but is locally destructive and invasive. It is likely to recur. The epidermoid carcinoma is a typical malignant tumor with local metastases early and distant metastases in the late stages. Five-year survivals free of tumor have been reported in 75 per cent of the basal cell carcinomas and in 70 per cent of the epidermoid carcinomas (Schrek). Grading of the tumors is a valuable aid in prognosis (Warren, Gates, and Butterfield).

Basal Cell Carcinoma

The basal cell carcinoma is characteristically a tumor of the face, nose, and ears. The

earliest change is the formation of a small, firm nodule in the dermis covered by unbroken skin. Gradually the nodule increases in size, and the typical "rodent" ulcer forms—a central excavated ulcer covered by shaggy ne-

of the ulcer there are invasion and destruction of the underlying tissues.) Thus in a basal cell carcinoma of the scalp the bones of the skull are eroded and opened. The greater part of the tumor is made up of circumscribed, inter-

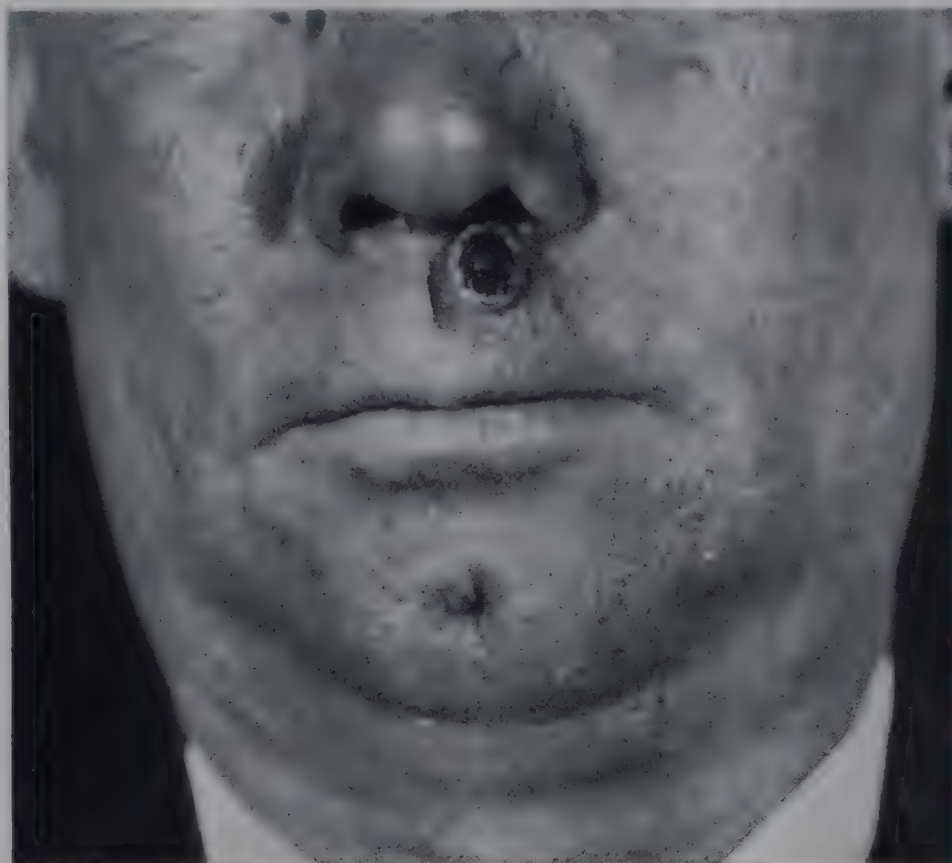


Fig. 497. Basal cell carcinoma of the upper lip. (Photograph from the files of the Barnard Free Skin and Cancer Hospital.)

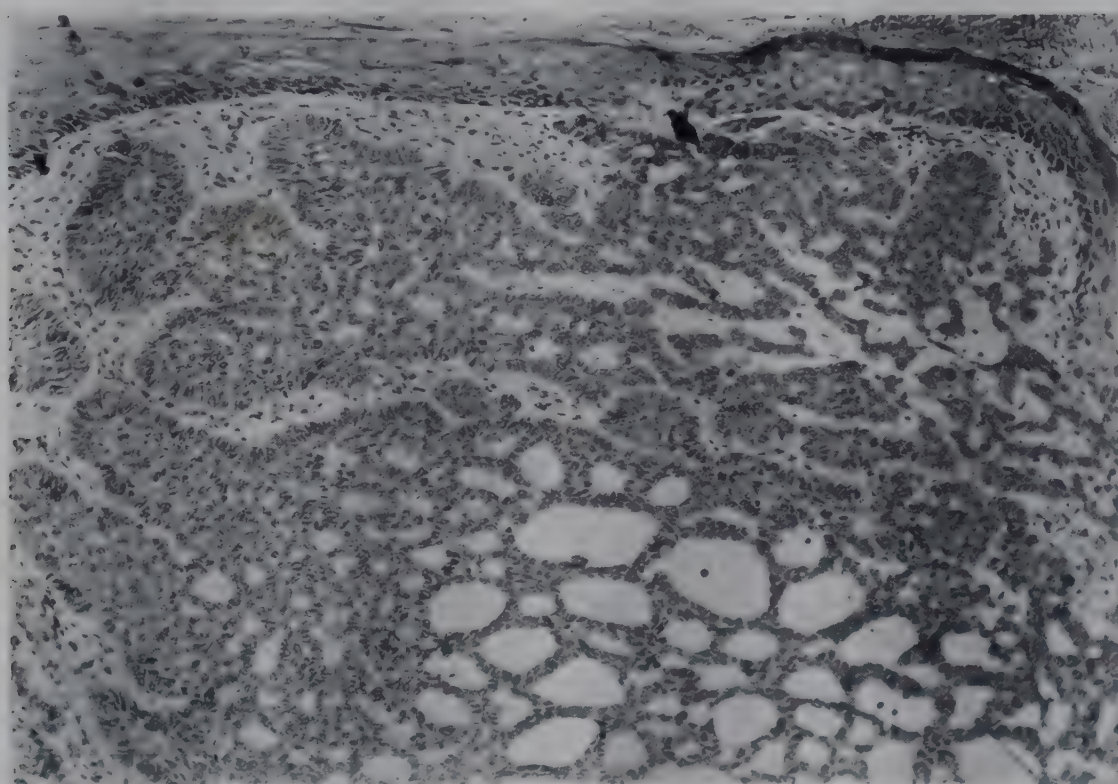


Fig. 498. Basal cell carcinoma of the cystic type. (Photograph by courtesy of Dr. Zola Cooper.)

crotic tissue and frequently by a purulent or serosanguinous exudate. The edges of the ulcer are elevated and firm. The induration extends into the surrounding tissue for a distance of one or more centimeters. In the base

communicating masses of small, darkly staining cells. The most peripheral cells in each nodule are columnar and oriented vertically to the basement membrane. The individual cells within the mass are small, polyhedral or spin-

dle shaped, with relatively large vesicular nuclei and a scanty cytoplasm. Keratinization and pearl formation are characteristically absent.

Histogenesis. Although the name "basal cell carcinoma" was given to this tumor because of the belief that it arises from the basal layer of the skin, this view has been questioned and an alternative hypothesis offered: that it is derived from the cells of the hair matrix. It is highly probable that both theories are correct, and that this tumor may originate from several types of cell (Montgomery).

Pigmented Basal Cell Carcinoma. In a rare basal cell carcinoma some of the cells contain granules of pigment, at times sufficient to produce gross pigmentation. In the surrounding stroma chromatophores are present. The prognosis is the same as in other types of basal cell carcinoma.

Epidermoid Carcinoma

There are two gross types of epidermoid carcinomas: one begins as an elevated, warty growth, and the other as a flat, indurated, infiltrating neoplasm. It is important to recog-



Fig. 499. Epidermoid carcinoma of the hand. (From the files of the Barnard Free Skin and Cancer Hospital.)

Mixed Forms of Cutaneous Epithelial Tumors. Not infrequently the histopathologist encounters tumors of the epidermis which in some areas are typical basal cell and in other areas are epidermoid carcinomas with keratinization and pearl formation. They should be treated as epidermoid carcinomas, although in general they carry a lower degree of malignancy than does the typical epidermoid carcinoma.

Cylindroma. The cylindroma, or "turban tumor," is a rare neoplasm, consisting of multiple, firm, nonulcerated nodes that encircle the scalp. Microscopically the individual epithelial cells appear similar to those of the basal cell carcinoma, but they are surrounded and separated by large and small masses and trabeculae of hyaline material (Ronchese).

nize the distinction between these two, since the first remains as a local though malignant tumor for many months or even years, while the latter is an invasive, metastasizing tumor in the early months of its growth. Cure may be easily effected in the first type if it is removed early.

Pathologic Anatomy. After the development of invasive growth in both types and the formation of a nodule exceeding 6 to 8 mm. in diameter, there is central ulceration. Microscopically the epidermoid carcinoma reproduces all layers of the normal epidermis in varying degree and amount. The cells typically are large, polyhedral cells with a large nucleus and a prominent nucleolus. Intercellular bridges are readily demonstrated, and there is no sharp basal layer separating the epithelium

from the surrounding stroma. In the center of many of the epithelial masses there is the characteristic epithelial pearl. This is a concentric structure, the most peripheral layers of which are made up of concentrically laminated, flattened, keratinized epithelium. In the center is a similarly laminated mass of fully keratinized cells with only an occasional pyknotic nucleus. In many epidermoid carcinomas there is secondary inflammation, characterized by infiltration with lymphocytes, polymorphonuclear leukocytes, or rarely eosinophils. The carcinoma that is ulcerated is likely to be more malignant than the carcinoma free of inflammation.

Histogenesis. There is little question that the epidermoid carcinoma takes origin directly from the epidermis by a down-growth from it. Histologic studies suggest that epidermoid carcinoma increases in size not only by growth but also by progressive cancerization of the immediately surrounding epidermis (Brunschwig and Tschetter).

The epidermoid carcinoma metastasizes to the regional lymph nodes in the early stages, and in the late stages to all parts of the body, particularly to the lungs and to the liver. The prognosis depends on the size and grade of the tumor and the presence or absence of metastases to the lymph nodes at the time of the primary operation or treatment with radiant energy (Warren and Hoerr).

Tumors of the Dermal Appendages

Tumors of the appendages of the skin differ from those originating in the surface epithelium. Warren, Gates, and Warvi recognize three major groups: from sebaceous glands, from sweat glands, and cystic tumors.

Tumors of Sebaceous Glands. It is difficult to distinguish between focal hypertrophy and hyperplasia of sebaceous glands and a benign tumor. There is little variation of the cells from normal in both. Multiple nodules on the face are known as adenoma sebaceum of the Balzar type. Pringle's disease consists of multiple congenital anomalies including focal hyperplasia of the sebaceous glands. Malignant tumors are observed. They are locally invasive, grow slowly, recur after removal, and metastasize late (Warren and Warvi).

Tumors of Sweat Glands. Gates, Warren, and Warvi differentiate four types: syringoma, papillary hidradenoma, solid hidradenoma,

and hidradenoid carcinoma. The cells of the syringoma closely resemble those of the normal coil duct. The papillary hidradenoma contains alveoli lined by a double layer, the luminal of which is columnar. The cells of the solid hidradenoma resemble basal cells. The diagnosis of carcinoma rests largely on local invasion as metastases are exceptional.

Cystic Tumors. Epithelial cysts may be differentiated on the basis of the cellular type in the lining into epidermal, sebaceous, sweat gland, and multiple follicular (pilosebaceous). Dermoid cysts occur. Epithelioma adenoides cysticum is a distinctive tumor occurring on the chest, axilla, and face, usually found in women at puberty and familial. Microscopically the tumors resemble sweat glands or hair follicles (Warvi and Gates).

Mesodermal Tumors of the Skin. Fibromas of the dermis are usually small and not encapsulated (Stecker and Robinson). They should be distinguished from the small accumulations of fibrous tissue with abundant elastic fibers, seen in the form of tumors in Ehlers-Danlos syndrome (Skeer and Kaplan). Leiomyomas occur in skin, and are probably derived from the cells of the arrector muscle of the hair or from the media of smaller blood vessels. They appear early in life and are likely to be multiple.

The keloid is not a true neoplasm, but represents extreme hyperplasia of fibrous tissue following injury. It is especially common in the colored race. It is to be distinguished from fibroma by the absence of elastic fibers. Keloids may grow to form large masses, but in general they increase in size slowly and reach a maximum after some months or years.

Nevus. Malignant Melanoma

These two tumors are composed of pigment-producing cells, and are benign and malignant respectively. Some tumors form abundant melanin and are grossly and microscopically pigmented, while other tumors form no melanin and the histopathologist must apply the dopa reaction to demonstrate the potentialities of the neoplastic cell.

Nevus. The term "nevus" should be used to designate only the tumor with a characteristic histologic structure. Thus the terms "vascular nevus," "angioid nevus," etc. should not be used. Grossly the nevus is a small, usually round, pigmented spot (nevus spilus), or a

soft, flat elevation, often with a warty excrescence (nevus verrucosus), or a papillary, pigmented tumor (nevus papillaris). Many exhibit a growth of soft or coarse hairs from the center or edge of the pigmented spot.

Microscopically two types are recognized—junction type and intradermal type. Mixture of the two are observed. In the junction type there are nests of clear cells at the dermo-epidermal junction (Traub and Keil). In the intradermal type there are nests of nevus cells in the dermis. Each nest is sharply demarcated from the surrounding tissue, but the entire tumor is not circumscribed, an appearance that should not be interpreted as malignant. Numerous unmyelinated nerves ramify between the cells. The significance of the various types of cells will be discussed under "Histogenesis."

Melanoma in Children. Tumors in children with all the histologic criteria of malignant melanoma are rarely malignant. Spitz observed giant cells in about half of juvenile melanomas which are not observed in adults. It is possible this behavior of melanomas in children is related to hormones.

Malignant Melanoma. About one-half of all malignant melanomas originate in a pre-existing nevus, while the other half start in the dermis without any previously demonstrable lesion. Grossly they are infiltrative, black masses of neoplastic cells, soft and friable. In the late stages there are metastases in the regional lymph nodes and in most of the viscera. The liver and the heart are frequently involved. Occasionally the primary tumor and more often the metastases are gray in color, and are called "amelanotic malignant melanomas." Microscopically the neoplastic cells are arranged in groups suggestive of the structure of a carcinoma. There is great variation in the shape of the cells—polyhedral, round, and spindle being the most common types. The cells in immediate contact with the connective tissue are usually oriented and contain more pigment than do the more centrally located cells. Nonmedullated nerve fibers are readily demonstrated. In melanomas of the eye the amount and character of the reticulum vary inversely with the degree of malignancy.

Histogenesis. The most frequent site for the malignant melanoma is the skin. Those who believe it is derived from the epithelium call it "melanocarcinoma," while those who believe

that the cell of origin is a mesoblastic chromatophore call it "melanosarcoma." Since both of these theories are incorrect, the noncommittal designation of "malignant melanoma" is to be preferred. Histologic demonstration of the presence of numerous nerve fibers and the similarity of the small and spindle shaped cells within the nevi and melanomas suggest that they are derived from the peripheral nervous system. Masson has demonstrated that the nevus and the malignant melanoma are derived from the cells of the peripheral nervous system, especially the tactile corpuscles of Merkel-Ranvier and the corpuscles of Meissner. Studies by Ewing, by Foot, and by Laidlaw have confirmed this postulation.

Incidence. Most nevi are present at birth, and Laidlaw believes that they are a carry-over of the lateral line organs of fish and reptiles into mammals. The average age for onset of malignant melanoma is about forty-five years, but they may be found at any age. The usual sites of origin are the face, leg, foot, back, neck, and arm. The blue nevus of Jadassohn and the Mongolian spot are rare forms of nevi.

Relation to Neurofibromatosis. Entirely aside from the neurogenic origin of the nevus and malignant melanoma, clinical and pathologic evidence supports a close relation with the nervous system. In von Recklinghausen's disease characteristic café au lait spots on the skin represent a disturbance in the distribution of pigment (p. 959). In persons with multiple nevi and melanomas, particularly the so-called "bathing trunk" type, there may be characteristic tumors on the deeper peripheral nerves. In both conditions, there is a hereditary influence.

Nondermal Melanoma and Melanomatosis. If the melanoma is derived from cells of the nervous system which migrate out from the neural tube in early embryonic life, it follows that the melanoma may be primary in many parts of the body. The only melanoma, beside that of the skin, which occurs frequently is that in the choroid coat of the eye. Rarely it is primary in the meninges, in the adrenal, or in the choroid plexus of the lateral ventricles (Foot and Zeck). The latter type sometimes occurs in children, and is known as melanomatosis (Wilcox).

Clinicopathologic Correlation. The malignant melanoma is one of the most malignant

tumors that occur in man. In the series of Farrell, 57 per cent of those with a primary operation at a time when there were no demonstrable metastases died in an average period of twenty-one months. Over half of these were related to a nevus. The indications of malignant change within a mole are an increase in size and pigmentation, bleeding, and the formation of satellite nodules about the larger primary tumor. Occasionally metas-

mation, and should not be mistaken for an inflammation with gangrene (Womack).

Hemangioma of the Skin

Several types of hemangioma of the skin are recognized. In the *capillary form* there is a well circumscribed, finely lobulated, bright red, elevated tumor in the superficial layers of the dermis. On pressure it does not bleach

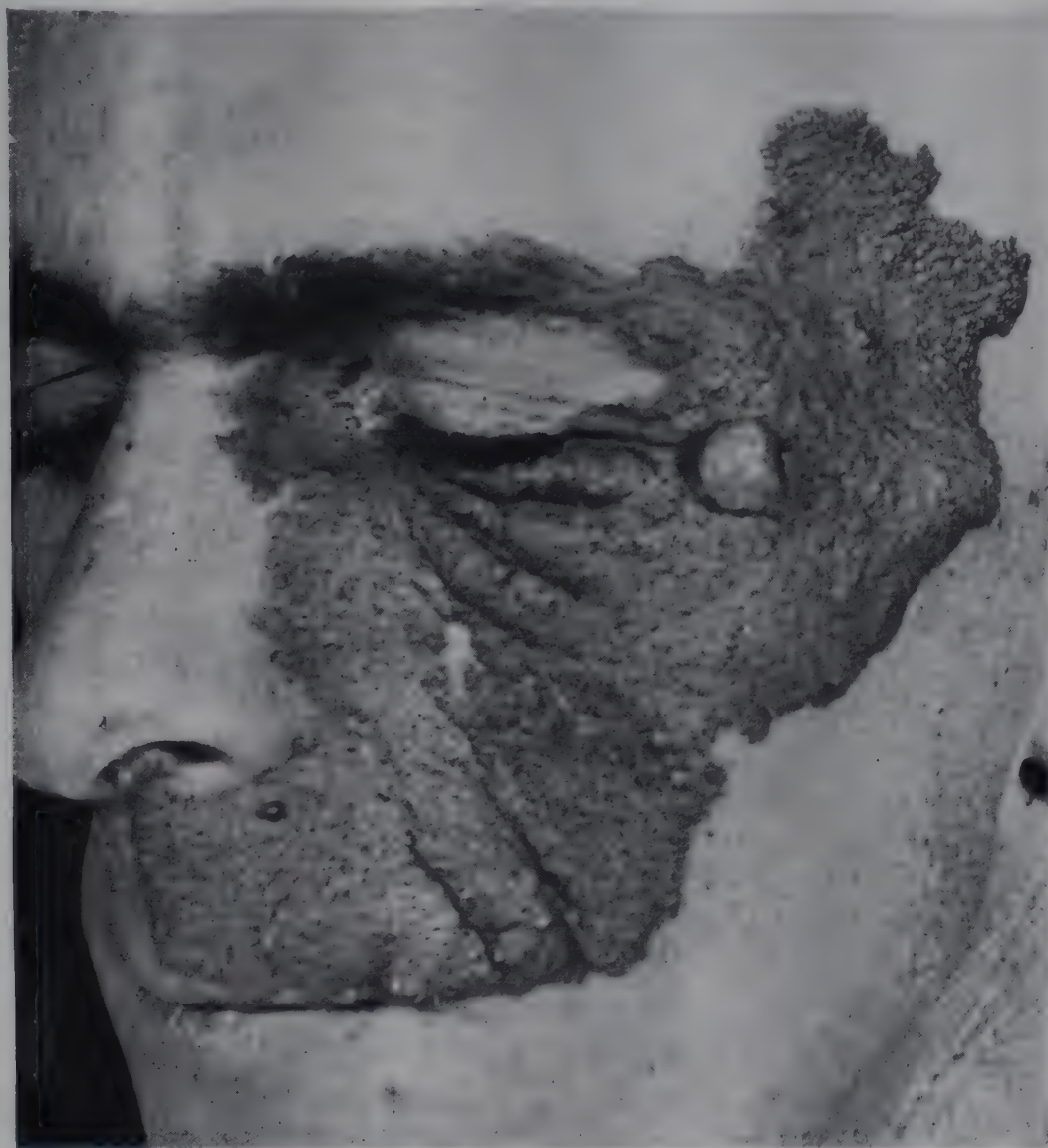


Fig. 500. Hemangioma of the face in a twenty-six-year-old man which had been present since birth. (From the files of the Barnard Free Skin and Cancer Hospital.)

tases are the first sign of a malignant melanoma, and it may require careful examination to find the primary tumor in one of the numerous pigmented nevi on the surface of the body (Butterworth and Klauder). The amelanotic tumors are in general more malignant than the pigmented types (Horwitz). The *subungual melanoma* or *melanotic whitlow* of Hutchinson is an especially malignant type of this tumor. It starts as a small pigmented spot on the lateral fold of the nail of either the finger or toe, rapidly enlarges and ulcerates. It shows many of the characters of an inflam-

completely. Microscopically it is made up of numerous small, well formed, capillary blood vessels, lined by endothelium, and separated from one another by a delicate connective tissue. Occasionally the capillaries are separated by fat or larger amounts of connective tissue and are designated incorrectly as "angiolipomas" and "angiofibromas." The *cavernous hemangioma* is composed of thin walled, widely dilated sinusoids lined by endothelium. It is soft, elevated, poorly circumscribed, and purple, and blanches on pressure. The *angio-blastic type* of hemangioma is a solid, elevated,

purplish red papule or plaque which cannot be compressed. Microscopically hyperplasia of the endothelium with occlusion of most of the vessels is seen. It should not be mistaken for a malignant tumor. The *port wine stain*, or *angioma vinosus*, consists of a few dilated sinusoids lined with endothelium in the dermis. There is no evidence of proliferation of the cells.



Fig. 501. Kaposi's disease. (Photograph from the files of the Barnard Free Skin and Cancer Hospital.)

Histogenesis. There is considerable doubt that the usual hemangioma of the skin is a neoplasm. It probably results from the sequestration of a small piece of mesenchyme during embryonic development. The vessels of a true angioma do not communicate with the surrounding vessels, and they are supplied by a single artery and drained by a single vein. Thrombosis of one of these is responsible for the spontaneous disappearance of some hemangiomas.

Incidence. About one-half of all hemangiomas of the skin are on the head, and most of these are on the face and scalp. With the ex-

ception of the port wine stain, which is predominantly a condition of men, the other hemangiomas show a sex preponderance in women of 3 to 1. The relation to the female phase of sex is further illustrated by the growth of hemangiomas at menstruation and during pregnancy, and by the well known telangiectasis of the palms of the hands in pregnant women, in patients with cirrhosis of the liver, and in persons receiving injections of estrogenic hormones. About 20 per cent of all hemangiomas are multiple, and over 75 per cent are present at birth or appear within the first few months of life.

Clinicopathologic Correlation. In general, hemangiomas grow at the same rate as the body as a whole grows, although some, especially the hyperplastic type, may start to increase in size at any time during life, invade the surrounding tissues, and behave as a locally malignant tumor. There are usually no signs or symptoms. The lesions merge imperceptibly into other more serious diseases. A large area of the body may be involved, such as an extremity or the pelvis, and the condition is then known as "diffuse systemic hemangioma." In other instances the tumors of the skin are associated with similar vascular anomalies of the retina and of the brain, termed Lindau's disease (p. 953). In addition there is a familial type, known as hereditary hemorrhage telangiectasia, or Rendu-Osler-Weber disease, marked by repeated hemorrhages from the mucous membranes, and telangiectatic nodules in the mucous membranes of the nose, mouth, viscera, and skin.

Lymphangioma. Most lymphangiomas appearing on the surface of the body are of the type known as "hygroma." These have been discussed in another chapter (p. 800). Occasionally small cystic nodules in the dermis prove on microscopic examination to consist of dilated lymph vessels. These probably represent congenital anomalies rather than true neoplasms (Watson and McCarthy; Ward and Covington).

Kaposi's Disease

The lesions of Kaposi's disease are spherical or plaque-like nodules, red or brown in color, on the surface of the skin, or occasionally in the mucous membranes, especially of the gastro-intestinal tract. They are more fre-

quent on the extremities than on the trunk, and in areas of skin directly over bone than over soft tissue. The nodules vary from a few millimeters to several centimeters in diameter, and do not coalesce. They are composed of large numbers of fibroblasts enclosing thin walled blood vessels. In some areas there is excessive collagen between the fibroblasts, while in others there is a delicate reticulum. The blood vessels are lined by a single layer of endothelium, and foci of hemorrhage are common. In some, at autopsy, similar nodules are found in all of the hollow and solid viscera of the body. Certainly for these the original name of "hemorrhagic sarcoma" is applicable. The spontaneous regression of some of the lesions of the skin, with a white or pigmented scar as the result, raises some question that this disease is truly neoplastic (Aegerter and Peale).

Causal Factors and Histogenesis. Kaposi's disease is more common in Jewish persons than in all others, and is rarely observed before the age of forty years. About 90 per cent of patients are men, usually manual laborers living under unfavorable urban conditions. The initial lesion appears to be a proliferation of the fibroblasts of the dermis immediately beneath the epidermis. Continued proliferation in a focal area leads to the formation of a nodule.

Clinicopathologic Correlation. The red or purple multiple nodules of the skin are usually not painful, and the patient consults a physician because of appearances rather than because of any symptom. The natural course of disease extends over many years, with the appearance of new nodules and the regression of older ones. Continued fibrosis leads to obliteration of the lymphatics and chronic lymphedema of a part or all of an extremity. Rarely the nodules ulcerate, usually as the result of trauma (Symmers).

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NOTE: Each disease and lesion is listed twice: under the name of the disease or lesion, and under the organ or tissue involved. The principal titles have been checked against the Subject Headings of the Quarterly Cumulative Index (Second edition, 1940) and all lesions described are listed as in that index or a cross reference is given. If there is a single item, the page numbers are printed rather than the cross reference in order to save the time of the reader. The well-established names of diseases are cited under the first word: thus, per-

nicious anemia is under P, and chronic ulcerative colitis under C. Other listings, however, are under anemia and bone marrow, and under colon, respectively.

The paragraph headings under each disease are not cited separately, but only the first page of the text devoted to the continuous consideration of a lesion or disease. Space thus saved is used for multiple listings under synonyms and under organs and tissues.

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